Universitat Internacional de Catalunya
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Tesi doctoral

Análisis de la función neuromuscular en el adulto mayor. Implicaciones en la valoración y la prescripción de ejercicio terapéutico.

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RESUMEN

Durante el envejecimiento se producen una serie de cambios fisiológicos que afectan en mayor o menor medida a la función neuromuscular. Concretamente se produce una disminución en la fuerza, en la cantidad y calidad muscular, y en el desempeño físico. Además, estos cambios son todavía mayores en condiciones patológicas, como la sarcopenia o el síndrome de fragilidad. En este sentido, la presente tesis doctoral expone dos líneas de investigación, ambas en torno a la función neuromuscular en el adulto mayor.

La primera línea de investigación tiene como objetivo evaluar el nivel de correlación entre las variables de fuerza muscular, desempeño físico y calidad muscular. Para ello, se llevaron a cabo 3 estudios observacionales. El primero, tenía como objetivo evaluar el nivel de correlación entre el máximo desplazamiento radial (Dm), valorado mediante tensiomiografía (TMG) y el stiffness, valorado mediante myotonometría (MMT). El segundo, evaluar el nivel de correlación entre los test funcionales para la evaluación de la fuerza y el desempeño físico, y los dispositivos de valoración de la calidad muscular; concretamente la TMG y la MMT. El tercer estudio observacional tenía como objetivo evaluar el nivel de correlación entre los test funcionales para la evaluación del desempeño físico, y el equilibrio estático valorado mediante estabilometría.

La segunda línea de investigación tiene como objetivo principal evaluar la efectividad de diferentes intervenciones en la fuerza muscular y el desempeño físico del adulto mayor. Para responder a este objetivo, se llevaron a cabo 4 revisiones sistemáticas y meta-análisis. En la primera se evaluó la efectividad del entrenamiento de fuerza en combinación con la suplementación proteica en comparación al entrenamiento de fuerza en solitario, para la mejora de la fuerza y el desempeño físico en adultos mayores. En la segunda se evaluó la efectividad del entrenamiento con restricción de flujo sanguíneo (BFRt), y en la tercera la efectividad del entrenamiento multicomponente (MCT). En el cuarto proyecto se evaluó la efectividad de diferentes modalidades de entrenamiento en la mejora del equilibrio estático.

Una vez llevados a cabo los proyectos anteriores, se realizó un estudio cuasiexperimental, mediante MCT en una población de adultos mayores, y se analizaron los cambios tanto en la fuerza, como en el desempeño físico, y en los parámetros de calidad muscular.

En cuanto a los resultados de los estudios observacionales, se encontró una correlación débil entre el Dm y el stiffness. Por otra parte, sólo las pruebas *Short Physical Performance Battery* (SPPB) y la prueba de sentarse y levantarse de la silla cinco veces (5XSST) mostraron correlaciones débiles-moderadas con los valores de Dm y stiffness. El nivel de correlación entre los valores de la estabilometría y las pruebas funcionales de SPPB, 5XSST y velocidad de marcha fue débil-moderado.

Los resultados obtenidos en el primer meta-análisis muestran que no existen diferencias en entre la combinación de entrenamiento de fuerza más suplementación proteica y el entrenamiento de fuerza en solitario para la mejora de la fuerza muscular y el desempeño físico en los adultos mayores sanos.

El segundo meta-análisis concluyó que el BFRt es efectivo para mejorar la fuerza muscular, sin embargo, no se encontraron diferencias significativas con otros tipos de entrenamiento en la mejora del desempeño físico.

El tercer meta-análisis concluyó que el MCT es efectivo en la mejora de la fuerza muscular y el desempeño físico.

El cuarto meta-análisis no encontró no mejoras en estadísticamente significativas en el equilibrio estático entre las diferentes modalidades de entrenamiento (entrenamiento de fuerza, entrenamiento aeróbico, entrenamiento de equilibrio y entrenamiento multicomponente).

Finalmente, el estudio de intervención mediante MCT mostró mejoras estadísticamente significativas en las pruebas funcionales de 5XSST, velocidad de marcha y fuerza de agarre. Sin embargo, en cuanto a la calidad muscular, no se mostraron mejoras en los parámetros de TMG y MMT, salvo en el stiffness del vasto lateral.

ABSTRACT

During aging, a series of physiological changes occur that affect to a greater or lesser extent neuromuscular function. Specifically, there is a decrease in strength, muscular quantity and quality, and physical performance. Furthermore, these changes are even greater under pathological conditions, such as sarcopenia or frailty syndrome. In this sense, the present doctoral thesis presents two lines of research, both focused on neuromuscular function in the older adults.

The first line of research aims to evaluate the level of correlation between variables of muscle strength, physical performance, and muscle quality. To achieve this, three observational studies were conducted. The first one aimed to evaluate the level of correlation between maximum radial displacement (Dm), assessed through tensiomyography (TMG), and stiffness, assessed through myotonometry (MMT). The second one aimed to evaluate the level of correlation between functional tests for the assessment of strength and physical performance, and devices for assessing muscle quality; specifically, TMG and MMT. The third observational study aimed to evaluate the level of correlation between functional tests for the assessment of physical performance and static balance assessed through stabilometry.

The second line of research aims to evaluate the effectiveness of different interventions in muscle strength and physical performance in older adults. To address this objective, four systematic reviews and meta-analyses were conducted. The first one evaluated the effectiveness of resistance training in combination with protein supplementation compared to resistance training alone, for the improvement of muscle strength and physical performance in older adults. The second one evaluated the effectiveness of blood flow restriction training (BFRt), and the third one evaluated the effectiveness of multicomponent training (MCT). The fourth project assessed the effectiveness of different training modalities in improving static balance.

After conducting the aforementioned projects, a quasi-experimental study was performed using MCT in a population of older adults, and changes in both strength and physical performance, as well as parameters of muscle quality were analyzed.

The results of the observational studies showed a weak correlation was found between Dm and stiffness. Moreover, only the Short Physical Performance Battery (SPPB) and the five times sit-to-stand test (5XSST) showed weak to moderate correlations with Dm and stiffness values. The level of correlation between stabilometry values and functional tests of SPPB, 5XSST, and gait speed was weak to moderate.

The results obtained in the first meta-analysis showed that there were no differences between the combination of resistance training plus protein supplementation and resistance training alone for improving muscle strength and physical performance in healthy older adults.

The second meta-analysis concluded that BFRt is effective for improving muscle strength, but no significant differences were found compared to other types of training in improving physical performance.

The third meta-analysis found that MCT is effective in improving muscle strength and physical performance.

The fourth meta-analysis did not find statistically significant improvements in static balance between different training modalities (resistance training, aerobic training, balance training, and multicomponent training).

Finally, the intervention study using MCT showed statistically significant improvements in functional tests of 5XSST, gait speed, and grip strength. However, regarding muscle quality, no improvements were shown in TMG and MMT parameters, except for the stiffness of the vastus lateralis.

ABREVIATURAS

5XSST: Five-Times Sit to Stand Test

ADN: ácido desoxirribonucleico

AMP: adenosín monofosfato

AMPK: AMP-activated protein kinase

ANZSSFR: Australian and New Zealand Society for Sarcopenia and Frailty Research

AT: Entrenamiento aeróbico

AVD: Actividades de la Vida Diaria

AWGS: Asian Working Group on Sarcopenia

BFR-t: Entrenamiento con restricción de flujo sanguíneo

BIA: Impedancia Bioeléctrica

BT: Entrenamiento de equilibrio

CRP: proteína C reactiva

CSA: Sección transversal muscular

CT: Tomografía computarizada

DHEA-S: andrógenos adrenales dehidroepiandrosterona sulfato

Dm: máximo desplazamiento radial

DXA: Absorciometría de rayos X de doble energía

EWGSOP: European Working Group on Sarcopenia in Older People

FNIH: Foundation for the National Institutes of Health

GH: Hormona de crecimiento

HIIT: entrenamiento de intervalos de alta intensidad

HPA: eje hipotálamo-pituitario-adrenal

IAGG: Asociación Internacional de Gerontología y Geriatría

IANA: Academia Internacional de Nutrición y Envejecimiento

IC: Intervalo de confianza

ICC: Coeficiente de Correlación Intraclase

ICD-10: Clasificación Internacional de Enfermedades en su 10ª edición

IGF-1: factor de crecimiento insulínico tipo 1

IL-6: interleuquina 6

IWGS: International Working Group on Sarcopenia

Kg: Kilogramos

MCT: Entrenamiento multicomponente

MeT: unidades metabólicas equivalentes

MMSE: Examen Mental Mini-Mental

MMT: Myotonometría

MRI: Resonancia magnética

MSC: células madre mesenquimales

mTOR: mammalian Target of Rapamycin

N: Newton

NAD+: nicotinamida adenina dinucleótido

OMS: Organización Mundial de la Salud

PS: Suplementación proteica

PT: Entrenamiento de potencia

ROS: especies reactivas del oxígeno

RM: Repetición máxima

RPE: Escala de esfuerzo percibido

RT: Entrenamiento de fuerza

s: segundos

SASP: fenotipo secretor asociado a la senescencia

SDOC: Sarcopenia Definitions and Outcomes Consortium

SEM: Error Estándar de la Media

SPPB: Short Physical Performance Battery

SWAG-SARCO: South Asian Working Action Group on SARCOpenia

Tc: Tiempo de contracción

Td: Tiempo de latencia

TMG: Tensiomiografía

TNFα: factor de necrosis tumoral alfa

Tr: Tiempo de relajación

Ts: Tiempo de mantenimiento de la contracción

TUG: Timed Up and Go

W: Watios

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INTRODUCCIÓN

ENVEJECIMIENTO

A lo largo de esta sección, se va a comenzar mostrando los diferentes cambios a nivel demográfico que se han producido en las últimas décadas relacionadas con el envejecimiento de la población. A continuación, se definirá qué se entiende por envejecimiento, y se explorarán los diferentes cambios fisiológicos que se producen tanto a nivel celular como a nivel de órganos y sistemas. Finalmente, se terminará explicando el concepto de *envejecimiento saludable*, así como una serie de términos relacionados que facilitarán al lector a comprenderla.

Cambios demográficos y epidemiológicos

Durante las últimas décadas, en todo el mundo, estamos viviendo un proceso acelerado de envejecimiento de la población (1). Organismos internacionales como la Organización Mundial de la Salud (OMS), o las propias Naciones Unidas han publicado recientemente varios reportes acerca de los cambios demográficos que se están produciendo.

Los informes globales de Naciones Unidas (1) muestran como actualmente el número de personas mayores de 60 años supera los 1000 millones de personas. Esta cifra supone el 13.5% de toda la población mundial. Además, se espera que, en los próximos 10 años, esta cifra aumente hasta los 1400 millones, alcanzando los 2100 millones a mediados de siglo. Dicho de otra manera, en 2017 una de cada ocho personas tenía 60 años de edad o más. En 2030 la proporción será de una de cada seis personas y, en 2050, una de cada cinco. Como dato remarcable, en 2020, el número de personas mayores de 60 años superó por primera vez al de niños menores de 5 años, y se espera que para dentro de 30 años, la proporción de personas mayores de 60 años duplique a la de 5. En cuanto a la distribución geográfica, la mayor parte de personas mayores viven en los denominados *países en desarrollo* y es en estos países donde el envejecimiento de la población es más acelerado, lo que supone un reto todavía mayor para esos países (2,3). En el Estado español, según el Instituto Nacional de Estadística (4), el porcentaje de personas mayores de 65 años fue del 20,1% del total en 2022, con perspectiva de incrementar hasta el 30,4% en torno a 2050.

En cuanto a las causas de este envejecimiento de la población, destacan principalmente el aumento de la esperanza de vida, así como la disminución de la natalidad (5). El aumento de la esperanza de vida se debe, en menor medida a un aumento de la supervivencia de las personas en edades avanzadas; aunque la causa principal se relaciona con un aumento en la supervivencia de las personas en edades más tempranas. En los países con menores recursos, la muerte tiende a producirse con mayor frecuencia en las primeras etapas de la infancia. A partir de entonces, las muertes se distribuyen de forma uniforme a lo largo del resto de la vida. A medida que los países se desarrollan, la mejora de la sanidad pública hace que un mayor número de personas sobreviva a la infancia, y el patrón de muertes se hace más frecuente en la etapa adulta. En los países con mayores ingresos, el patrón de muerte se desplaza aún más hacia la vejez, de modo que la mayoría de las muertes se producen en personas mayores de 70 años. Las principales causas de muerte en los adultos mayores son las enfermedades no transmisibles. Sin embargo, tanto en los países de ingresos bajos como en los de ingresos medios, las enfermedades transmisibles siguen siendo una causa importante de muerte a lo largo de la vida. En referencia a España, la esperanza de vida al nacer es una de las más altas del mundo, con los últimos datos oficiales de 2019 reflejando una media de 80,9 años en hombres y 86,6 en mujeres. Estos datos sitúan a nuestro país en el primer lugar de la Unión Europea y tercero a nivel mundial, solo superada por Japón y Suiza (6).

Fisiología del envejecimiento

Una vez documentados los cambios en la demografía de la población asociados al envejecimiento, resulta indispensable definir qué se entiende por este fenómeno. El envejecimiento es un proceso caracterizado por una pérdida progresiva de la integridad fisiológica, a causa de la acumulación de daño celular, que conlleva un deterioro de las funciones y en última estancia una mayor vulnerabilidad ante la muerte (7).

En este sentido, el Dr. Carlos López-Otín (8) hace ya casi una década, describió 9 marcadores que influyen de manera interrelacionada en el envejecimiento. Estos marcadores son: la inestabilidad genómica, el acortamiento de telómeros, las alteraciones epigenéticas, la pérdida de proteostasis, la desregulación de la detección de nutrientes, la disfunción mitocondrial, la senescencia celular, el agotamiento de las células madre y la alteración de la comunicación intercelular.

- Inestabilidad genómica

La inestabilidad genómica es la tendencia a la acumulación de daño en el material genético a lo largo de la vida (9). La integridad y la estabilidad del ADN se ven continuamente amenazadas tanto exógenas como endógenas. Entre las amenazas exógenas encontraríamos agentes físicos, químicos y biológicos del exterior; y entre las endógenas destacan los errores de replicación del ADN, las reacciones hidrolíticas[1] espontáneas y los radicales libres[2] con capacidad de producir daños oxidativos denominados *especies reactivas del oxígeno* (ROS) (10,11). Las lesiones genéticas derivadas de estas amenazas son diversas, e incluyen mutaciones puntuales, translocaciones[3], ganancias y pérdidas cromosómicas, acortamiento de los telómeros[4] y alteraciones genéticas causadas por la integración de virus en el material genético. Para minimizar estas lesiones, los organismos han desarrollado una compleja red de mecanismos de reparación del ADN que, en conjunto, son capaces de hacer frente a la mayoría de los daños infligidos al ADN nuclear (12). Sin embargo, con el paso del tiempo, estos mecanismos de reparación del ADN pierden eficacia, pudiendo provocar alteraciones del ADN que afecten tanto a los genes como a las vías de transcripción, dando lugar a células disfuncionales que, si no se eliminan por apoptosis[5] o senescencia[6], pueden poner en peligro la homeostasis de los tejidos y órganos. Esto es especialmente relevante cuando los daños en el ADN afectan a la competencia funcional de las células madre, comprometiendo así su papel en la renovación de los tejidos (8).

[1] Reacciones en las que una sustancia se rompe en componentes más simples por reacción con moléculas de agua.
[2] Especie molecular sin carga caracterizada por tener un electrón desapareado en un orbital atómico. Esta característica la hace altamente reactiva y de vida corta.
[3] Desplazamiento de un segmento de un cromosoma a un nuevo lugar en la secuencia de ADN.
[4] Son regiones de ADN situadas en los extremos de los cromosomas. Estas regiones son altamente repetitivas y no codifican secuencias de proteínas, sino que su función principal es la estabilidad estructural de los cromosomas
[5] Muerte celular programada de las células dañadas.
[6] Detención irreversible el crecimiento y la división celular como resultado del envejecimiento celular

- Acortamiento de telómeros

En relación a lo anterior, la acumulación de daños en el ADN con la edad parece afectar al genoma de forma casi aleatoria, pero hay algunas regiones cromosómicas que son particularmente susceptibles al deterioro relacionado con la edad (8). Concretamente, a lo largo de las sucesivas divisiones celulares, la longitud de los telómeros disminuye de forma natural hasta alcanzar un tamaño mínimo crítico, que impide la continuación de la división celular, provocando la senescencia celular (13).

- Alteraciones epigenéticas

La epigenética hace referencia a los mecanismos de regulación genética que no implican modificaciones en las secuencias de ADN. Estos cambios heredables facilitan la adaptación a las señales del entorno y definen las características fenotípicas estables de los distintos tipos de células (14). De entre estos mecanismos destaca la metilación del ADN, proceso mediante el cual se añaden grupos metilo al ADN, actuando generalmente como inhibidores de la transcripción genética. Por su parte, el envejecimiento genera alteraciones en los patrones de metilación del ADN (hiper/hipo metilación) que perturban la expresión genética (8).

- Pérdida de proteostasis

Todas las células desarrollan una serie de mecanismos de control de calidad para preservar la estabilidad y funcionalidad de sus proteomas[7] (15). Esta regulación homeostática de las proteínas se denomina *proteostasis*, e incluye principalmente mecanismos para la estabilización de las proteínas correctamente plegadas y para la

[7] Conjunto de proteínas que se expresan o pueden expresarse a partir del genoma de una célula, tejido u organismo.

degradación de las proteínas por los proteasomas[8] o los lisosomas[9]. Todos estos sistemas funcionan de forma coordinada para restaurar la estructura de los polipéptidos mal plegados o para eliminarlos y degradarlos completamente, evitando así la acumulación de componentes dañados y asegurando la renovación continua de las proteínas intracelulares (15). Existe evidencia de que el envejecimiento se asocia a la perturbación de la proteostasis, contribuyendo al desarrollo de ciertas patologías relacionadas con la edad (8).

- Desregulación de la detección de nutrientes

Nuestro organismo dispone de diferentes vías de señalización, que nuestras células utilizan para detectar la cantidad de nutrientes presentes en el organismo. Entre las diferentes vías destacan la vía de señalización de la insulina y el factor de crecimiento similar a la insulina 1 (IGF-1) para la detección de la glucosa, la vía mTOR (de sus siglas en inglés mammalian Target of Rapamycin) para la detección de aminoácidos, la vía AMPK (de sus siglas en inglés AMP-activated protein kinase) para la señalización de bajos niveles de energía a través de la detección adenosín monofosfato (AMP), y las sirtuinas, que señalizan niveles de baja energía detectando de nicotinamida adenina dinucleótido (NAD+) (11). La acumulación de daños celulares con el paso del tiempo (por alteraciones en el ADN, el acortamiento de telómeros etc.) y el estrés oxidativo (consecuencia de la disfunción mitocondrial), sumada a la sobreestimulación de las vías por el exceso de nutrientes terminaría generando una alteración en las vías de señalización. Como resultado, los

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[8] Complejo proteico grande presente en todas las células eucariotas que se encarga de realizar la degradación de proteínas no necesarias o dañadas

[9] Orgánulo celular de forma irregular y membrana sencilla que contiene reservas de enzimas necesarias para la digestión de las partículas ingeridas por las células fagocitarias

mecanismos de crecimiento y reparación de los daños celulares pueden verse afectados, favoreciendo el envejecimiento celular (8).

- Disfunción mitocondrial

Las mitocondrias son orgánulos que se encuentran en todas las células humanas y su función principal es la producción de energía mediante la fosforilación oxidativa[10]. La acumulación de daño mitocondrial con el paso del tiempo provoca una disminución de la eficacia de este proceso, reduciendo la generación de ATP y aumentando así la fuga de electrones, que generan especies reactivas del oxígeno (ROS) (14). Actualmente, no existe un consenso claro sobre el papel de las ROS en el envejecimiento. Aunque los radicales libres suelen estar implicados en el daño celular y la inflamación cuando están presentes en niveles elevados, también pueden aumentar potencialmente las defensas celulares mediante una respuesta adaptativa (mitohormesis) cuando están presentes en niveles más bajos (16). En este sentido, el principal efecto de las ROS será la activación de respuestas homeostáticas compensatorias. A medida que avanza la edad cronológica, el estrés y el daño celular acumulado aumentan, y los niveles de ROS se incrementan paralelamente en un intento de mantener la supervivencia. Más allá de un determinado umbral, los niveles ROS dejan de producir su propósito homeostático original y acaban agravando, en lugar de aliviar, los daños asociados a la edad (8).

- Senescencia celular

La senescencia celular se define como una detención estable del ciclo celular unida a cambios fenotípicos secretores específicos (17). La principal causa de

[10] Proceso metabólico que utiliza energía liberada por la oxidación de nutrientes para producir ATP.

senescencia celular es el acortamiento telomérico, aunque hay otros estímulos asociados al envejecimiento que podrían desencadenan este proceso, como el daño en el ADN, el estrés oxidativo, o el deterioro de los mecanismos de autofagia (17). Dado que el número de células senescentes aumenta con el envejecimiento, se ha asumido ampliamente que la senescencia contribuye al envejecimiento. Sin embargo, esta visión deja de lado lo que podría ser el objetivo biológico principal de la senescencia, que sería el de evitar la propagación de las células dañadas y desencadenar su desaparición mediante el sistema inmunitario (8). Por lo tanto, es posible que la senescencia sea una respuesta compensatoria beneficiosa que contribuye a librar a los tejidos de células dañadas y potencialmente oncogénicas (17). Sin embargo, para ello se requiere un sistema eficiente de reemplazo celular que implique la eliminación de células senescentes y la movilización de progenitores para restablecer el número de células. En los organismos envejecidos, este sistema de recambio puede volverse ineficaz o agotar la capacidad regenerativa de las células progenitoras, dando lugar finalmente a la acumulación de células senescentes que pueden agravar el daño y contribuir al envejecimiento (17). En los últimos años, se ha observado que las células senescentes manifiestan alteraciones en su secretoma[11], con altas concentraciones de citoquinas proinflamatorias y metaloproteinasas de la matriz[12]. Este secretoma proinflamatorio se denomina "fenotipo secretor asociado a la senescencia" (SASP) y podría ser una de las causas del envejecimiento (18).

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[11] Conjunto de proteínas, consecuencia de la expresión génica de una célula, tejido u organismo, que son secretado al espacio extracelular. En humanos, este tipo de proteínas abarca un 13-20% de todas las proteínas e incluye a citoquinas, factores de crecimiento, matrices extracelulares etc. Si el secretoma tiene características predominantemente proinflamatorias, en ocasiones se denomina también "inflamasoma".

[12] Familia de encimas encargadas de la degradación de proteínas en el medio extracelular.

- Agotamiento de células madre

La disminución del potencial regenerativo de los tejidos es una de las características más evidentes del envejecimiento (8). En este sentido, el agotamiento de las células madre desempeña un papel fundamental, ya que interfiere con la autorrenovación de las células diferenciadas de los tejidos y órganos, reduciendo paulatinamente su función (19). Una vez más, el declive de las células madre surge como consecuencia de diferentes tipos de daños interrelacionados, entre los que destacan la acumulación de daños en el ADN, la sobreexpresión de proteínas inhibidoras del ciclo celular o el acortamiento de los telómeros (20). Un buen ejemplo es el declive de la hematopoyesis[13] relacionado con la edad, que provoca una disminución de la producción de células inmunitarias adaptativas, lo que se conoce como *inmunosenescencia* (8). Además, se han encontrado procesos similares en diferentes compartimentos de células madre adultas, incluyendo el cerebro, el hueso o las fibras musculares (8). De hecho, el tipo de célula madre más afectado durante el envejecimiento podría ser el que tiene capacidad de generar tejido muscular (miogénesis), conocido como células satélite (20). La reducción en el número o la funcionalidad de estas células miogénicas impide el mantenimiento adecuado de la masa muscular (21). En concreto, la atrofia por envejecimiento de las fibras musculares de tipo II[14] va acompañada de una disminución específica del contenido de células satélite de las fibras musculares de tipo II (15). Finalmente, aunque la proliferación deficiente de células madre es perjudicial para el mantenimiento del

[13] Proceso de formación, desarrollo y maduración de los elementos de la sangre a partir de un precursor celular común e indiferenciado conocido como célula madre hematopoyética multipotente.
[14] El músculo se compone de fibras de tipo I y tipo II. Las fibras de tipo I (de contracción lenta) poseen una mayor capacidad oxidativa debido a su mayor densidad de mitocondrias y capilares, y están compuestas principalmente por la isoforma de la cadena pesada de miosina (MHC) tipo I. Las fibras de tipo II (de contracción rápida) poseen una mayor capacidad glucolítica y se pueden subdividir en fibras de tipo IIA y tipo IIB, que están compuestas principalmente por MHC2a y MHC2x, respectivamente.

organismo a largo plazo, una proliferación excesiva también podría ser perjudicial, al acelerar el agotamiento de los nichos de células madre, conduciendo a un envejecimiento prematuro (8).

- Alteración de la comunicación intercelular

Más allá de las alteraciones autónomas de las células, el envejecimiento también implica alteraciones en los mecanismos de comunicación intercelular, ya sea endocrina, neuroendocrina o neuronal. En última instancia, este envejecimiento se acompaña de un fenotipo proinflamatorio denominado *inflammaging* (22), y que se caracteriza por una inflamación crónica de bajo grado, de carácter sistémico, y en ausencia de infección (inflamación estéril) (23,24). Esta inflamación puede deberse a múltiples causas, como la acumulación de daños tisulares proinflamatorios, la incapacidad de un sistema inmunitario cada vez más disfuncional para eliminar eficazmente los patógenos y las células disfuncionales (inmunosenescencia), y la propensión de las células senescentes a secretar citoquinas proinflamatorias (SASP) (8).

Tal y como nos propone López-Otín, podemos dividir estos marcadores en 3 categorías diferentes: marcadores primarios, marcadores antagonistas, y marcadores integradores (8). Los marcadores primarios se caracterizarían por ser claramente negativos, y comprenderían la inestabilidad genómica, el acortamiento de los telómeros, las alteraciones epigenéticas y la pérdida de proteostasis. Los marcadores antagonistas se caracterizarían por tener efectos opuestos según la intensidad. En un inicio, a bajos niveles tendrían beneficios positivos, pero a altos niveles, o cuando se cronifican, su efecto sería subvertido, y generarían más daño. Entre ellos se incluirían la desregulación de la detección de nutrientes, la disfunción mitocondrial y la senescencia celular. En última instancia, los marcadores integradores se caracterizan por afectar directamente a la homeostasis y a la función de los tejidos. Entre ellos encontraríamos la el agotamiento de las células madre y la alteración de la comunicación intercelular (8). A pesar de que existe una interrelación entre los diferentes marcadores, se propone una cierta relación jerárquica entre los mismos, siendo los marcadores primarios los desencadenantes iniciales, favoreciendo la desregulación de los marcadores antagonistas. Finalmente, los marcadores integradores surgirían cuando el daño acumulado causado por los marcadores primarios y antagonistas no pudiera ser compensado por los mecanismos homeostáticos de los tejidos (8).

La *Figura 1* recoge los marcadores del envejecimiento explicados anteriormente, divididos según si se tratan de marcadores primarios, marcadores antagonistas, y marcadores integradores. Además, debajo de cada uno de los marcadores, sintetiza los cambios fisiológicos que caracterizan a cada uno de ellos.

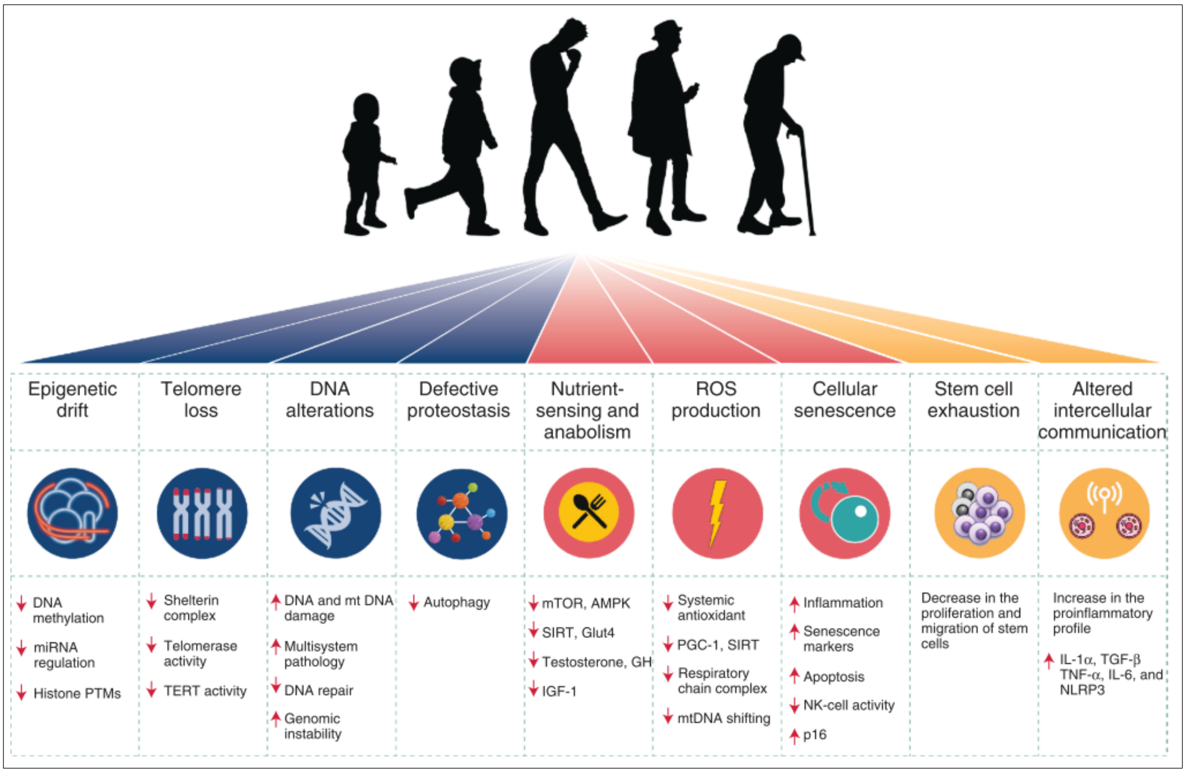

Figura 1: Marcadores de envejecimiento. Adaptado de Valenzuela et al. 2019 (25)

Una vez explicados los procesos fisiológicos que se hayan detrás del envejecimiento celular, procederemos a explicar cómo estos cambios afectan al conjunto de tejidos y órganos en lo que respecta a los principales sistemas relacionados con el movimiento.

Cambios en el Sistema Neuromuscular

A partir de los 50 años, la cantidad de masa muscular disminuye cada año aproximadamente entre 1-2%. Además, la fuerza muscular lo hace un 1.5% a partir de los 50 años, y un 3% a partir de los 60 años (26). Por último, la capacidad de realizar fuerza en poco tiempo (potencia muscular) disminuye todavía más rápido que la fuerza (27). En cuanto a la disminución de la masa muscular, como ya se ha comentado, el principal factor parece ser la disminución en el recambio de proteínas musculares, debido a una menor actividad anabólica relacionada con el envejecimiento (21). Sin embargo, respecto a la disminución de la fuerza y la potencia muscular, parece que también influyen otros factores tanto cuantitativos como cualitativos relacionados con la masa muscular y la función neuromuscular (28). A nivel neuromuscular, el envejecimiento se acompaña de una pérdida de motoneuronas α, así como de una reinervación incompleta de las fibras musculares previamente denervadas. Además, el envejecimiento se relaciona con una reducción tanto en la tasa de transporte axonal[15], como en la velocidad de conducción nerviosa (28). Por otro lado, los cambios en la estructura muscular que se produce durante el envejecimiento contribuyen a la pérdida de la función muscular. De entre estos cambios destaca la infiltración intramuscular de tejido no contráctil, ya sea grasa o colágeno (28). Además, el envejecimiento da como resultado la atrofia de las fibras musculares, especialmente en las fibras de contracción rápida o tipo II, así como una conversión de fibras de tipo II a tipo I, que a su vez conduce a una disminución de la fuerza máxima y la capacidad de producción de potencia (28). Finalmente, algunas propiedades de la arquitectura muscular también pueden variar con el envejecimiento. Por ejemplo, con el envejecimiento, en algunos músculos disminuyen el grosor y el ángulo de penación (25).

Cambios en el Sistema Cardiorespiratorio

El envejecimiento genera una disminución gradual de la función cardiorrespiratoria, medida comúnmente mediante el consumo máximo de oxígeno de un individuo (VO2max) (29). Con la edad, se produce reducción del gasto cardíaco máximo,

[15] También denominado transporte axoplásmico o flujo axoplásmico, es el proceso celular responsable del movimiento de mitocondrias, lípidos, vesículas sinápticas, proteínas y otros orgánulos hacia y desde el cuerpo celular de neurona, a través del citoplasma de su axón llamado el axoplasma.

resultado de una disminución en el volumen sistólico máximo y la frecuencia cardíaca, así como cambios en la diferencia arteriovenosa de oxígeno (30). La función pulmonar también se ve comprometida progresivamente con el envejecimiento, debido principalmente a un aumento en la rigidez de la pared torácica y una disminución en la fuerza de los músculos respiratorios (como el diafragma y los músculos abdominales), lo que se manifiesta mediante una disminución del volumen espiratorio forzado (30). Además, la presión arterial parcial de oxígeno disminuye progresivamente debido a un desajuste de ventilación-perfusión inducido por la edad (30). Finalmente, disminuye el área de superficie alveolar disponible para el intercambio de gases debido a cambios en la geometría interna del pulmón durante el envejecimiento (30).

La *Figura 2* sintetiza los principales cambios fisiológicos que se producen con el envejecimiento tanto a nivel celular, como a nivel de órganos y sistemas.

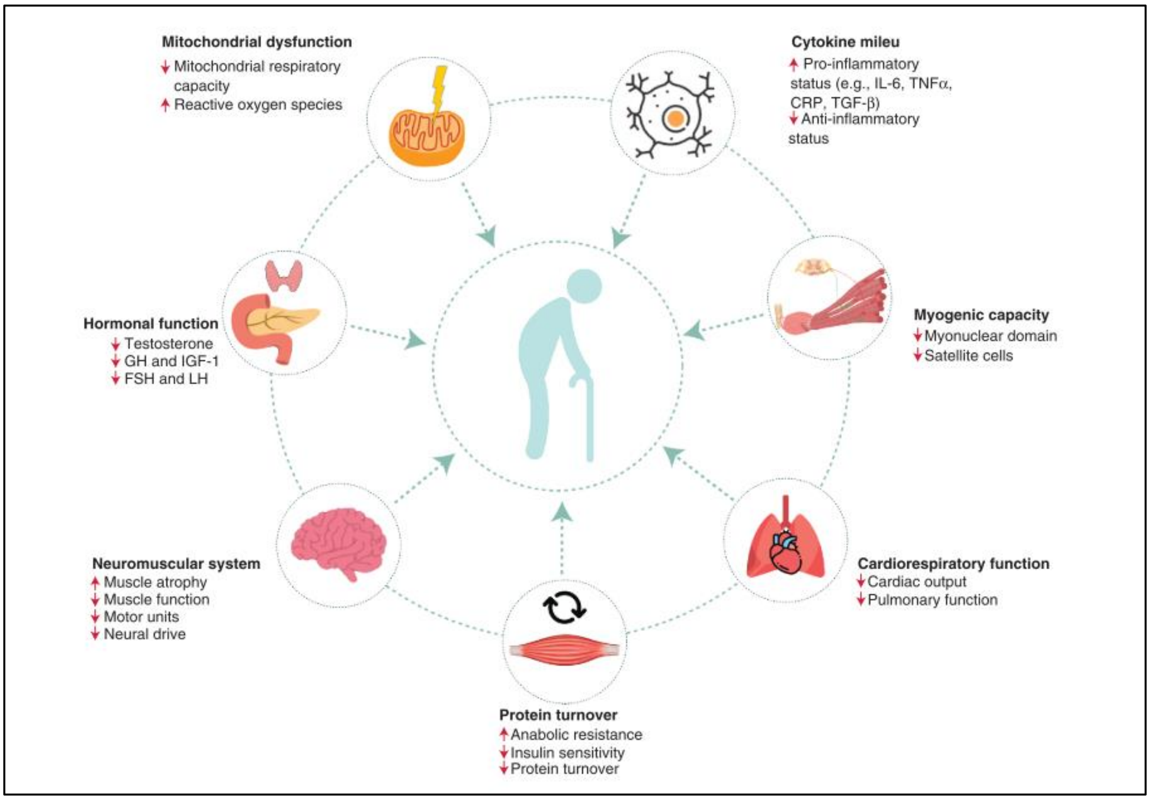

Figura 2: Cambios fisiológicos asociados al envejecimiento. Adaptado de Valenzuela et al. 2019 (25)

Envejecimiento Saludable

El concepto de *envejecimiento saludable* ha ido evolucionando desde mediados del siglo pasado hasta 2015, cuando la OMS definió envejecimiento saludable no solo como la ausencia de enfermedad durante la vejez; sino como *"el proceso de desarrollar y mantener la capacidad funcional que permite bienestar*[16] *en la vejez"* (31). A su vez, propusieron un nuevo modelo de explicar el envejecimiento saludable, en el que introdujeron los conceptos de *capacidad intrínseca*, *entorno*, *capacidad funcional* (5). A continuación, se explicará cada concepto, para después comentar las diferentes interrelaciones que existen entre ellos, y que conforman la trayectoria de envejecimiento de cada persona.

[16] Percepción subjetiva de tener una vida satisfacción, en equilibrio y armonía tanto en el ámbito físico, como emocional y socioeconómico.

En primer lugar, tenemos la capacidad intrínseca, que hace referencia al conjunto de todas las capacidades físicas y mentales de un individuo en un momento determinado de su vida. En este sentido, podría considerarse una medida de las reservas fisiológicas[17] del individuo (32). La capacidad intrínseca incluye a su vez 5 grandes dominios totalmente interrelacionados entre sí, y que pretenden abarcar las diferentes capacidades del individuo: el desempeño físico[18] (marcha, equilibrio y fuerza muscular), la cognición (memoria, inteligencia, y resolución de problemas), la vitalidad[19] (función hormonal, función cardio-respiratoria y metabolismo energético), el estado psicológico (estado de ánimo y vitalidad emocional) y las capacidades sensoriales (vista, oído, olfato, gusto y tacto) *(Figura 3)* (33,34).

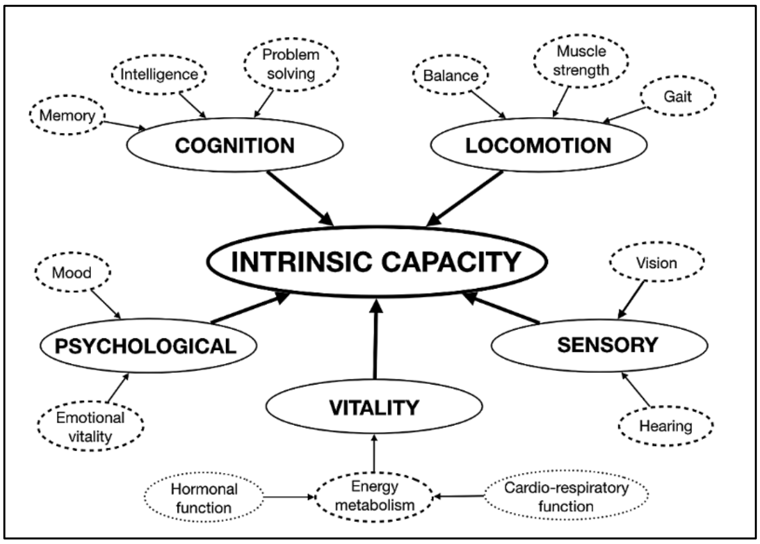

Figura 3: Dominios de la Capacidad Intrínseca. Adaptado de Chhetri et al. 2021 (34)

La capacidad intrínseca viene fuertemente marcada por nuestra herencia genética, aunque la expresión de estos genes puede verse influida incluso antes de nacer por

[17] Capacidad potencial de una célula, tejido o sistema orgánico para funcionar por encima de su nivel basal, como respuesta a alteraciones de las demandas fisiológicas producidas por estresores internos o externos.
[18] Capacidad del individuo para deambular y realizar transferencias. Involucra no sólo la función muscular, sino el sistema nervioso, e incluye la capacidad de equilibrio.
[19] Conjunto de funciones corporales dedicadas a metabolizar la ingesta alimentaria con el fin de producir la cantidad de energía necesaria para el mantenimiento de un nivel homeostático óptimo.

el entorno del útero y las exposiciones ambientales y comportamientos de la madre. A partir del nacimiento, la expresión genética se ve influida tanto por los factores ambientales como por los comportamientos propios del individuo (esto es lo que se conoce como cambios epigenéticos[20]) (35). Además, cada persona vive en un entorno social, y en él desarrolla una serie de características personales, algunas fijas, como el sexo o la etnia, y otras variables, como el trabajo, nivel educativo, o la riqueza. Estas características personales conforman la posición social del individuo dentro de un contexto y tiempo particular, lo que a su vez condicionará el tipo de exposiciones, oportunidades, recursos y barreras a las que éste se enfrenta, ya sea de manera justa o injusta (5). A lo largo de la vida, la exposición acumulada a esta variedad de factores ambientales, influirá en el desarrollo de diferentes características de salud, en forma de factores de riesgo fisiológicos (presión arterial alta, nivel de colesterol etc.), lesiones previas (caídas, fracturas etc.), enfermedades (enfermedades cardiometabólicas, etc.) y síndromes geriátricos más amplios (fragilidad, etc.). Finalmente, será la interacción entre las diferentes características de salud la que determinará, en última instancia, la capacidad intrínseca del individuo (36).

Como ya se ha comentado, en el concepto de envejecimiento saludable, además de la capacidad intrínseca, destaca el concepto de entorno. El entorno hace referencia a todos los elementos del mundo extrínseco que forman el contexto de la vida de un individuo, ya sea a nivel del hogar, de la comunidad o de la sociedad en general (5). Cada entorno se encuentra modulado por una serie de factores entre los que destacan el entorno físico construido; las personas que lo conforman, con sus

[20] La epigenética es el estudio de los mecanismos que regulan la expresión de los genes sin que exista una modificación en la secuencia del ADN que los compone. Establece la relación entre las influencias genéticas y ambientales que determinan un fenotipo.

relaciones, actitudes y valores; las políticas sanitarias y sociales que los rigen; y los sistemas económicos que las apoyan (5).

Por último, la capacidad intrínseca de cada persona, las características del entorno en el que vive y las interacciones que realiza el individuo con ellas, dan como resultado su capacidad funcional. En este sentido, la capacidad funcional hace referencia a los atributos relacionados con la salud que permiten a cada persona ser y hacer lo que ella considera importante en un momento determinado de su vida. Así pues, el hecho de que un adulto mayor sea capaz de realizar aquellas cosas que él mismo valora, no sólo depende de su capacidad intrínseca, sino que, una vez más, está condicionada por la interacción con el entorno en el que habita esa persona (5). Por ejemplo, una persona con una limitación en su capacidad intrínseca que limita su movilidad podrá realizar una determinada tarea dependiendo de si se encuentra en un entorno que le favorece, ya sea por medios económicos que le permitan acceder a un dispositivo de ayuda (andador, silla de ruedas etc.), por un sistema sanitario que los financie, por un entorno familiar que pueda acompañarla, por un entorno físico con ausencia de barreras arquitectónicas etc.

La *Figura 4* sintetiza el modelo de envejecimiento saludable explicado anteriormente, con los conceptos de capacidad intrínseca, capacidad funcional, entorno y las diferentes interacciones entre estos tres conceptos. Además, dentro de la capacidad intrínseca no sólo está determinada por la herencia genética, sino que está constituida por las características de salud y las características personales.

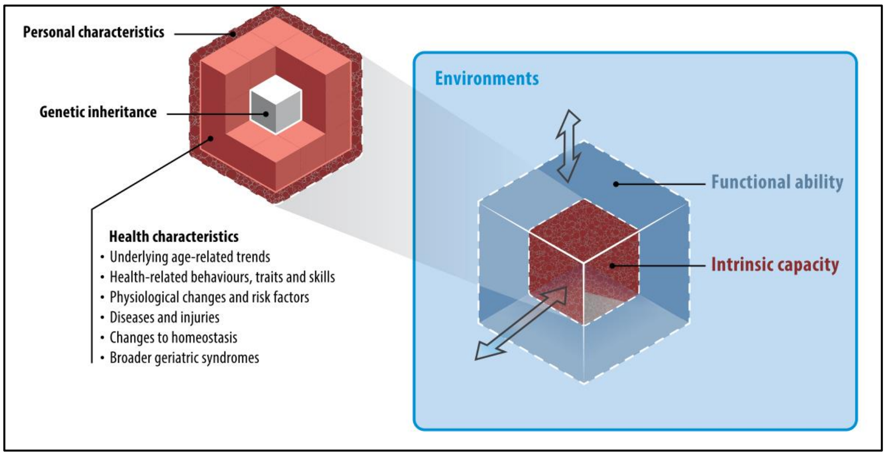

Figura 4: Determinantes del envejecimiento saludable. Adaptado de WHO 2015 (5)

Como se ha comentado en la primera sección de la presente tesis doctoral, el envejecimiento se caracteriza por la acumulación de daño celular, lo que se traduce en una disminución de las reservas fisiológicas del individuo, provocando un mayor riesgo de sufrir determinadas enfermedades, discapacidad y, en última instancia, la muerte. Así pues, la tendencia habitual es que la capacidad intrínseca disminuya con la edad, sin embargo, esta disminución no se produce de manera lineal a lo largo del tiempo, ni lo hace de igual manera en todas las personas (5). De la misma manera, la capacidad funcional también tiende a disminuir, aunque no lo hace de manera proporcional a la capacidad intrínseca, ya que quedará fuertemente influida por el entorno en el que se encuentre el individuo (*Figura 5*). En cualquier momento dado, una persona puede tener reservas de capacidad funcional a las que no está recurriendo. Estas reservas contribuyen a la resiliencia[21] de una persona mayor (34). Además, tanto la capacidad intrínseca como la capacidad funcional son constructos

[21] Capacidad de mantener, recuperar o mejorar un nivel de capacidad funcional al ser sometido a un factor estresor u adversidad. Tanto el concepto de resiliencia, como el de capacidad intrínseca se centran en atributos positivos de la salud del adulto mayor, a diferencia de otros constructos, como el de fragilidad, centrado en la acumulación de déficits funcionales. Es decir, buscan pasar de un paradigma centrado en la enfermedad hacia paradigmas centrados en la función. Por su parte, la principal diferencia entre la resiliencia y la capacidad funcional radica en que, para establecer la resiliencia de una persona, es necesario definir el estresor específico ante el que la persona debe exponerse.

dinámicos, y tienen cierta reversibilidad si se realizan intervenciones tanto en el individuo como en el entorno. En las primeras etapas del envejecimiento, se deberían fomentar estrategias que ayudasen a mantener o incluso mejorar la capacidad intrínseca del individuo lo máximo posible (mejorar la alimentación, la actividad física, el descanso etc.), y cuando no fuese posible, en edades biológicas avanzadas, fomentar cambios en el entorno que mantuviesen la capacidad funcional lo máximo posible (5).

La *Figura 5* sintetiza la trayectoria habitual de la capacidad intrínseca y de la capacidad funcional a lo largo de los años. Como puede observarse, la disminución de ambas no es proporcional, especialmente en las últimas etapas de la vida, donde las modificaciones en el entorno pueden mantener la capacidad funcional de la persona.

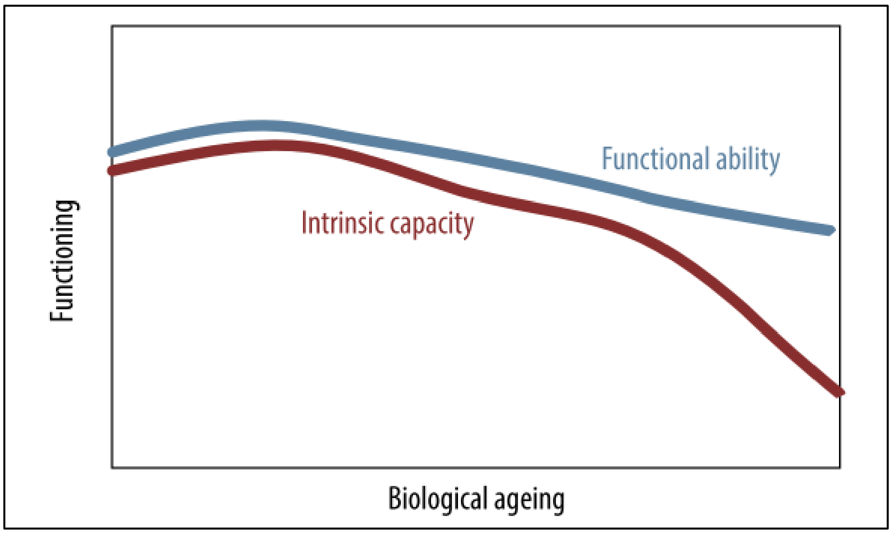

Figura 5: Trayectorias de la Capacidad Funcional y la Capacidad Intrínseca. Adaptado de WHO 2015 (5)

SÍNDROME DE FRAGILIDAD

Una vez descrita la fisiología del envejecimiento, los cambios demográficos, y los conceptos relacionados con el envejecimiento saludable, esta sección va a centrarse en el síndrome de fragilidad. Primeramente, se definirá el concepto de fragilidad, y cómo éste ha ido evolucionando a lo largo de los años. Seguidamente, se abordará su epidemiología, así como los eventos negativos asociados y el coste que supone. Por último, se detallarán los aspectos relacionados con su fisiopatología, explicando uno por uno sus diferentes determinantes.

Definición y Antecedentes

El síndrome de fragilidad se describe como un estado clínico caracterizado por un declive progresivo de los diferentes sistemas, que generan una disminución de las reservas fisiológicas y un aumento en la vulnerabilidad ante un estrés tanto interno como externo (37). Este estado clínico aumenta el riesgo de sufrir eventos adversos, como caídas y lesiones, hospitalización, discapacidad, dependencia y en última estancia, la muerte (38).

En el pasado, el síndrome de fragilidad se concebía únicamente como un factor determinante de la edad biológica del individuo. Se daba por sentado que, a partir de cierta edad, el individuo se volvía más vulnerable ante los estresores a los que era sometido. Sin embargo, esta idea se refutó al observar clínicamente que la respuesta de los pacientes ante una enfermedad, su estado funcional y su supervivencia no dependían únicamente de la edad, sino de las reservas fisiológicas del organismo. La visión actual del síndrome de fragilidad sugiere que éste no es una parte inevitable de los procesos fisiológicos del envejecimiento y que por tanto no se aplica a todas los adultos mayores, y que sin embargo puede aparecer en poblaciones no geriátricas (39). Basándose en este marco conceptual, en las últimas décadas, han surgido principalmente dos herramientas de evaluación de la fragilidad. Estas son el *Fenotipo de Fragilidad* y el *Índice de Fragilidad* (40). A continuación, se va a proceder a describir cada una de ellas.

En el año 2001, Fried y colaboradores (37) describieron el *Fenotipo de Fragilidad* o *Fenotipo de Fried* mediante la presencia de al menos tres de los siguientes criterios: debilidad, medida por la baja fuerza de agarre; lentitud, por la disminución de la velocidad al caminar; bajo nivel de actividad física; baja energía o agotamiento autodeclarado; y pérdida de peso involuntaria. Además establecieron un estado de "pre-fragilidad" cuando se cumplieran 1-2 de los criterios (41). A pesar de ser una herramienta especialmente útil en el ámbito clínico, algunos autores destacan que se trata de una herramienta unidimensional, centrándose únicamente en la dimensión física de la fragilidad (42,43). Por contra, cabe destacar que este instrumento concibe la fragilidad como una entidad clínica distinta de otras dos condiciones prevalentes en personas mayores, como son la discapacidad, (medida por la disminución en las actividades de la vida diaria) y la multimorbilidad (definida por la presencia simultánea dos o más enfermedades crónicas en un mismo individuo) (44). Estas tres condiciones (fragilidad, discapacidad y multimorbilidad) son predictivas en diferentes grados de resultados adversos de la salud y, por lo tanto, tienen cierto nivel de solapamiento. Sin embargo, las características principales de la fragilidad, como son la disminución de la reserva funcional, la disfunción o la desregulación en múltiples sistemas fisiológicos y la reducida capacidad de recuperar la homeostasis fisiológica después de un evento estresante, hacen que la distinción de la fragilidad sobre la discapacidad o la multimorbilidad sea relativamente fácil utilizando esta herramienta diagnóstica (41). Aunque muchas personas frágiles son discapacitadas, no todas las personas discapacitadas son frágiles (45). Por ejemplo, los pacientes mayores que sufren una discapacidad grave secundaria a un accidente o un derrame cerebral grave pueden mantener una función relativamente intacta en otros sistemas fisiológicos y, por lo tanto, no son frágiles. La multimorbilidad indica la presencia de múltiples enfermedades crónicas (45). No es sorprendente que la multimorbilidad esté asociada con un mayor riesgo de resultados clínicos adversos, como se demuestra por una mayor mortalidad a corto y largo plazo y una discapacidad física significativamente aumentada en comparación con aquellos sin enfermedades. Sin embargo, la mera presencia de dos o más diagnósticos clínicos en sí mismos no puede identificar al grupo vulnerable de pacientes mayores o aquellos que son frágiles (45).

Por su parte, Rockwood y colaboradores (46) propusieron el *Índice de Fragilidad* como una acumulación de diferentes déficits, incluyendo deficiencias físicas y cognitivas, factores de riesgo psicosociales, y otras enfermedades y síndromes geriátricos distintos de la fragilidad. De esta manera, a diferencia del *Fenotipo de Fragilidad*, se trata de un modelo de fragilidad multidimensional, ya que no se centra únicamente en la dimensión física (43). A su vez, en comparación con el *Fenotipo de Fragilidad*, el *Índice de Fragilidad* parece ser un predictor más sensible de eventos adversos para la salud, debido a que incluye una escala de riesgo más precisa, y a que incorpora déficits que probablemente tengan relaciones causales con los eventos clínicos adversos (43,47). Sin embargo, aunque el *Índice de Fragilidad* puede tener una utilidad clínica en la evaluación de riesgo y estratificación, no está claro si agrega valor significativo a una evaluación geriátrica integral (41). Además, el *Índice de Fragilidad* no distingue la fragilidad de la discapacidad o la comorbilidad, a diferencia del *Fenotipo de Fragilidad* (41). En su lugar, las incluye a ellas o a sus déficits asociados. Asimismo, contar el número de déficits acumulados no constituye un síndrome geriátrico clínico en sí mismo. Finalmente, el *Índice de Fragilidad* dificulta investigar los mecanismos subyacentes y etiología de la fragilidad (41). Es por eso que muchos avances recientes en la patogénesis de la fragilidad se basan en la definición de *Fenotipo de Fragilidad* (41), aunque existe cierta controversia sobre cuál de ellos es más sensible en la predicción de la fragilidad (47–49).

Con todo, se han hecho esfuerzos importantes a nivel internacional para alcanzar un consenso sobre la fragilidad. Aunque todavía no se ha acordado una definición operacional o herramienta de evaluación simple, se ha establecido un consenso de que la fragilidad 1) es un síndrome clínico, 2) indica una mayor vulnerabilidad a los estresores, lo que conduce a un deterioro funcional y resultados adversos para la salud, 3) puede ser reversible o atenuada por intervenciones y 4) detectar la fragilidad es útil en atención primaria (50).

Epidemiología

La prevalencia del síndrome de fragilidad en la población geriátrica es un fenómeno de carácter mundial, estando presente en millones de adultos mayores de todo el mundo (38). Sin embargo, la prevalencia global sigue siendo incierta, debido principalmente al predomino de estudios realizados en países de ingresos elevados, así como a la heterogeneidad en la definición del síndrome de fragilidad y en los instrumentos de medida utilizados (38). Una revisión sistemática que incluyó 21 estudios, agrupando un total de 61.500 adultos mayores residentes en comunidades de países de ingresos altos encontró una estimación promedio del 10.7% (IC 95% 10.5–10.9%) para la prevalencia de fragilidad, pero a su vez evidenció una variabilidad enorme en la misma, con un rango del 4% al 59% de prevalencia entre los estudios (51). Además, se han identificado niveles elevados de prevalencia de fragilidad en subgrupos específicos, incluyendo adultos mayores en centros institucionalizados (52.3%, IC 95% 37.9-66.5) (52), personas infectadas con VIH (5-28.6%) (53), pacientes con enfermedad renal en estado terminal (36.8%, IC 29.9-44.1%) (54) y pacientes con tumores sólidos o hematológicos (42%, rango 6%–86%) (55). Se ha observado un patrón general en el que la prevalencia de fragilidad es mayor en mujeres que en hombres y aumenta con la edad, así como también se ha documentado una asociación entre un estatus socioeconómico bajo y pertenencia a minorías étnicas con una mayor prevalencia de fragilidad (56).

En España, existen pocos trabajos que estudien la prevalencia del síndrome de fragilidad. Sin embargo, un reciente estudio realizado en 2021 en 408 participantes, con una edad media de 79.8 años, siendo la mayoría mujeres (59.1%), encontró una prevalencia de fragilidad del 27.7%. Además, analizando los factores asociados a la misma, relacionaron la fragilidad con una alta comorbilidad, polifarmacia, percepción de calidad de vida con la salud, dificultades para caminar, riesgo de caídas, dependencia para las actividades diarias, discapacidad, deterioro cognitivo y depresión (57).

Fragilidad y riesgo de eventos adversos

La fragilidad es un importante factor de riesgo de mortalidad en adultos mayores (58). La asociación entre fragilidad y mortalidad ha sido confirmada en muchos estudios y en diferentes entornos y subpoblaciones (58–60). Concretamente, una revisión sistemática encontró que el riesgo de mortalidad aumentó de manera gradual con el aumento del número de componentes fenotípicos de fragilidad (es decir, cuanta mayor puntuación según el *Fenotipo de Fragilidad*) o déficit presentes acumulados (es decir, cuanto mayor era su puntuación según el *Índice de Fragilidad*) (61). La fragilidad también está relacionada con una amplia gama de otros eventos, como discapacidad (62), caídas (63), fracturas (64), empeoramiento de la movilidad (65), soledad (66), baja calidad de vida (67), depresión (68), declive cognitivo (69,70), demencia (71), hospitalización (72) y admisión en centros institucionalizados (38).

Coste de la fragilidad

El impacto de la fragilidad en los gastos y uso de atención médica ha sido objeto de recientes investigaciones (73–76). Aunque los diferentes estudios son difíciles de comparar en cuanto a población estudiada, tamaño de la muestra e instrumentos de medición utilizados; en general reflejan un patrón claro de aumento en los costes y uso de atención médica asociado con la fragilidad (73–76). Especialmente, este aumento de los costes relacionado con la fragilidad se manifiesta en un mayor uso de atención médica en los sectores de atención hospitalaria, subaguda y ambulatoria (38). Concretamente, en España, un trabajo publicado de 2017 observó a 830 adultos mayores de 70 años en Albacete (77). El coste individual promedio de los recursos de salud fue de 1,922€ por año. Por su parte, los participantes frágiles tenían un coste total promedio de 2,476€ por año, frente a los 1,217€ por año en los no frágiles (77). Respecto a su distribución, el 67% del coste total de salud fue asociado con la admisión hospitalaria, el 29% con el coste de visitas a especialistas y el 4% con el coste de visitas de emergencia (77).

Fisiopatología

De manera general, el síndrome de fragilidad se origina principalmente por un desequilibrio metabólico del organismo y una disfunción de los sistemas inmunológico y neuroendocrino (78). La fisiopatología del síndrome de fragilidad se asemeja (y a menudo se superpone) con el proceso de envejecimiento fisiológico. Sin embargo, en la fragilidad, existe un mayor desequilibrio en el metabolismo de energía, que genera un continuo estado catabólico. Además, los procesos combinados de senescencia celular, desregulación de la detección de nutrientes y disfunción mitocondrial (descritos en la primera sección de la presente tesis doctoral) juegan un papel clave tanto a nivel celular como molecular (39). Todos estos procesos influyen en el desarrollo del síndrome de fragilidad a través de la desregulación en el funcionamiento de los órganos y sistemas (39). El estado de *inflammaging* en el síndrome de fragilidad se vuelve todavía más predominante (22). Esta inflamación crónica de bajo grado induce a catabolismo, lo que resulta en una redistribución de aminoácidos desde los músculos esqueléticos, que a su vez lleva a una pérdida significativa de fuerza y masa muscular (79). La presencia de otras enfermedades crónicas (como la insuficiencia cardíaca) y los procedimientos quirúrgicos contribuyen adicionalmente a la estimulación de del sistema inmunológico, induciendo a un mayor estado proinflamatorio (22). Esto se manifiesta con niveles elevados de citoquinas proinflamatorias, como la interleuquina 6 (IL-6), además de otras moléculas inflamatorias como la proteína C reactiva (CRP) o el factor de necrosis tumoral alfa (TNFα) (23). A su vez, estas citoquinas proinflamatorias favorecen la degradación de proteínas, o afectan indirectamente las vías metabólicas (24). Asimismo, los pacientes con síndrome de fragilidad presentan entre otras, una baja concentración de vitamina D, una disminución de la concentración de hormonas sexuales y de crecimiento, y una secreción anormal de cortisol, influyendo una vez más en el estado proinflamatorio (39,41). Es importante entender que estos procesos no se producen de manera lineal, unidireccional y secuencial, sino que todos estos cambios se superponen entre ellos, de manera multidireccional y generan bucles de retroalimentación. En base al artículo de Wleklik y colaboradores (39), se va a proceder a describir los principales factores determinantes en la aparición de la fragilidad:

Malnutrición

El estado nutricional anormal del paciente es un factor importante entre los determinantes de la fragilidad (80). Concretamente, la pérdida de apetito/anorexia del envejecimiento es un síndrome geriátrico propio altamente prevalente y problemático que afecta negativamente la calidad de vida de los adultos mayores (81). La pérdida de apetito está asociada con varias condiciones clínicas, incluyendo comorbilidades y otros síndromes geriátricos, como la fragilidad (81). Al igual que en este último, el control del apetito también está influenciado por varios determinantes a diferentes niveles, incluyendo factores fisiológicos (por ejemplo, ageusia[22] y el anosmia[23] relacionadas con la edad), determinantes patológicos (por ejemplo, depresión, demencia, medicamentos, mala higiene dental y deglución, y otras enfermedades crónicas), e incluso determinantes sociales (por ejemplo, soledad, pobreza, inseguridad alimentaria) (81). La malnutrición contribuye a la reducción de masa muscular y fuerza, lo que afecta el desempeño físico del cuerpo. La malnutrición podría contribuir a un menor nivel de actividad física, lo que a su vez generaría una disminución en el apetito, pudiendo retroalimentar el estado de malnutrición (82). Además, la malnutrición aumenta la disfunción del sistema inmunológico, reduciendo la resistencia a las infecciones (83). En líneas generales, parece que la anorexia relacionada con el envejecimiento y la pérdida de peso asociada tienen un papel importante en la fisiopatología de la fragilidad (83). En este sentido, la pérdida de peso en personas mayores suele ser involuntaria (83). Según el enfoque del *Fenotipo de Fragilidad*, uno de los criterios diagnósticos de esta patología estaría determinado por una pérdida de peso involuntaria de más de 4,5 kg o ≥5% en el último año (37).

Polifarmacia

El término polifarmacia es utilizado en la literatura para describir el uso simultáneo de múltiples fármacos por parte de un paciente, concretamente cinco o más (84). Aunque la polifarmacia puede ser adecuada y estar totalmente justificada, a menudo se le ha dado una connotación negativa y se ha utilizado para expresar la condición perjudicial definida por la prescripción de uno o más fármacos que el paciente no

[22] La ageusia hace referencia a la pérdida total del gusto. Por su parte, la hipogeusia hace referencia a la pérdida parcial del gusto.
[23] La anosmia hace referencia a la pérdida total del olfato. Por su parte, la hiposmia hace referencia a la pérdida parcial del olfato.

necesita o ha dejado de necesitar. Los cambios relacionados con la edad en la farmacocinética[24] y farmacodinamia[25] de los medicamentos, así como la multimorbilidad, hacen que la prescripción de medicamentos para los ancianos sea un desafío clínico, generando un aumento en la probabilidad de equivocarse en la dosificación de medicamentos y la consecuente ocurrencia de efectos adversos, como caídas, hospitalización e incluso muerte (84). Además, este consumo injustificado de medicamentos afecta a la sostenibilidad del sistema sanitario público a través de mecanismos directos (por ejemplo, el coste de los medicamentos innecesarios) e indirectos (por ejemplo, las hospitalizaciones debidas a reacciones adversas) (85). De hecho, incluso cuando un medicamento no tiene efectos nocivos aparentes, su prescripción inadecuada puede tener consecuencias perjudiciales al complicar la terapia del paciente o afectar negativamente a su estado de ánimo (por ejemplo, haciéndole sentir enfermo y vulnerable) (85).

Como se ha comentado anteriormente, la fragilidad se caracteriza por una disminución en la reserva fisiológica del organismo, que lo convierte en más vulnerable frente a diferentes estresores tanto endógenos como exógenos, entre los que podríamos incluir a los medicamentos. En este sentido, la polifarmacia es un factor de riesgo común, potencialmente modificable, en el desarrollo de la fragilidad en los adultos mayores (86). Por una parte, genera efectos negativos en las enfermedades ya existentes. Además, actúa sobre otros factores característicos del fenotipo de fragilidad, por ejemplo, favoreciendo la pérdida de peso. Finalmente, los efectos secundarios relacionados con la polifarmacia a menudo llevan a la denominada "cascada de prescripción", en la que se prescriben nuevos

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[24] Estudio del movimiento de los medicamentos hacia el interior, a través del organismo y hacia el exterior de este, es decir, el curso temporal de su absorción.
[25] Estudio de los efectos bioquímicos y fisiológicos de los fármacos y de sus mecanismos de acción y la relación entre la concentración del fármaco y el efecto de éste sobre un organismo.

medicamentos para contrarrestar los efectos adversos de los medicamentos hasta ahora tomados (86).

La polifarmacia, a pesar de ser una entidad altamente prevalente entre los adultos mayores, suele estar poco estudiada, ya que las personas mayores, especialmente las frágiles o con varias comorbilidades, parecen ser excluidas de ensayos clínicos aleatorios, lo que dificulta todavía más sus elecciones terapéuticas (85). Algunos autores defienden que parte de la medicina "tradicional" todavía aborda la enfermedad de manera aislada en el tratamiento del paciente, lo que a menudo provoca que cada patología se considere y trate de manera individual (85). Este error sería particularmente relevante en personas frágiles que presentan multimorbilidad y viven en una situación de vulnerabilidad extrema, donde una receta equivocada podría representar el factor estresante exógeno que precipite al individuo a experimentar eventos adversos de su estado de fragilidad. Al mismo tiempo, este enfoque a menudo olvida que las prioridades del paciente pudieran no ser las mismas que las del médico prescriptor (85). Por contra, el aumento de las enfermedades crónicas discapacitantes relacionadas con la edad hace que el enfoque en la preservación de la funcionalidad sea mucho más relevante en comparación con el tratamiento de la enfermedad específica (85). Así pues, el individuo frágil no tendría por qué considerar como primordial el tratamiento de una enfermedad diagnosticada, sino que podría considerar la mantención de la autonomía y la independencia como su prioridad (85).

Síntomas depresivos

La depresión es considerada como uno de los principales determinantes de la fragilidad en los adultos mayores (68). De hecho, un estudio en población española refleja que la prevalencia de la depresión en adultos mayores con fragilidad se encuentra alrededor del 40.4% (87). La depresión aumenta en hasta cuatro veces el riesgo de fragilidad (OR 4.07, IC 95% 1.93- 8.55), y a su vez las personas frágiles tienen más probabilidades de desarrollar depresión (OR 3.94, IC 95% 2.36- 6.58) (88). Los síntomas de la depresión a menudo se solapan con los de la fragilidad, y pueden ser difíciles de identificar clínicamente. Entre ellos, destacarían la disminución de la actividad diaria, la disminución del apetito, o el aislamiento social (39,68). A su vez, la literatura también describe la relación entre el tratamiento antidepresivo y el aumento de la incidencia de fragilidad en mujeres mayores (39).

Existe una creciente evidencia que respalda el papel de la inflamación crónica de bajo grado como un mecanismo responsable tanto de la depresión como de la fragilidad en los adultos mayores (89). Actualmente se cree que los procesos inflamatorios podrían promover cambios en los sistemas neuronales del cerebro que predisponen a algunas personas a desarrollar depresión geriátrica. Entre estas citoquinas proinflamatorias, niveles elevados de IL-6 han estado consistentemente asociados con síntomas depresivos significativos y trastornos depresivos en personas mayores (89). Por otra parte, la desregulación del eje hipotálamo-pituitario-adrenal (HPA) de hormonas también se ha propuesto como posible etiología tanto de la depresión como de los síndromes de fragilidad en adultos mayores. Concretamente, los niveles bajos de andrógenos adrenales dehidroepiandrosterona sulfato (DHEA-S) y factor de crecimiento insulínico tipo 1 (IGF-1) están asociados con la fragilidad y la depresión. Finalmente, otros posibles factores etiológicos tanto de la depresión como de la fragilidad en personas mayores incluyen la reducción de la testosterona relacionada con la edad o las fluctuaciones diarias de cortisol (68).

Trastornos cognitivos

Los trastornos cognitivos están considerados como uno de los predictores del síndrome de fragilidad (69). Los datos clínicos sugieren una relación clara entre la fragilidad y las alteraciones cognitivas leves, la demencia, la disminución cognitiva en la edad avanzada y el Alzheimer (69–71). Además, las personas con trastornos cognitivos tienen un mayor riesgo de discapacidad, dependencia y hospitalización (39).

A menudo, en la investigación científica, la fragilidad física y el deterioro cognitivo suelen estudiarse por separado. Sin embargo, para comprender mejor la relación entre estas dos condiciones y para promover nuevas investigaciones que apoyen intervenciones de carácter multidisciplinar, la Academia Internacional de Nutrición y Envejecimiento (IANA), en colaboración con la Asociación Internacional de Gerontología y Geriatría (IAGG) definieron en el año 2013 el concepto de *fragilidad cognitiva*, ampliando la definición de fragilidad física para incluir el aspecto cognitivo. La fragilidad cognitiva fue definida como a una manifestación clínica heterogénea que se caracteriza por la presencia simultánea de fragilidad física y deterioro cognitivo en el adulto mayor (90).

Los determinantes tanto de las alteraciones cognitivas en el adulto mayor, como de la fragilidad a menudo se solapan. Algunos de estos determinantes incluyen factores tanto biológicos, como psicológicos o socioeconómicos. En cuanto a los determinantes biológicos, se encontraría la edad avanzada, el sexo femenino o la presencia de comorbilidades, entre las que destacarían afecciones cardiovasculares (diabetes, dislipidemias e hipertensión), las deficiencias nutricionales o la inactividad física. En cuanto a los determinantes psicológicos, destacan los síntomas de depresión, el uso de medicamentos u otras drogas, y una baja percepción de la salud. Finalmente, entre los determinantes sociales destacarían el bajo nivel de educación y de ingresos económicos, el aislamiento social o la viudedad (91). A pesar de todo, el principal punto de unión entre los trastornos cognitivos y la fragilidad podría encontrarse, una vez más, en la inflamación crónica de bajo grado (92). Finalmente, a pesar de que las anomalías estructurales del cerebro subyacentes a la fragilidad física no están del todo claras, parece ser que el fenotipo de fragilidad, a nivel del encéfalo, podrían ser consecuencia de una reducción del volumen total del cerebro y especialmente de la materia gris; además del aumento de los infartos cerebrales corticales (33). Tanto en el ámbito clínico como en investigación, existen herramientas para identificar la disminución cognitiva en pacientes con fragilidad, como el Examen Mental Mini-Mental (MMSE) (93).

Falta de apoyo social

Las relaciones sociales son importantes para la salud. En este ámbito, la mayoría de las investigaciones se han centrado en los conceptos de aislamiento social y la soledad (66). El aislamiento social se define objetivamente utilizando criterios tales como tener pocos contactos, poca participación en actividades sociales y vivir solo (94). Por su parte, la soledad es una sensación subjetiva de insatisfacción con las relaciones sociales en el momento actual (94). Tanto el aislamiento social como la soledad se han relacionado con un aumento del deterioro funcional, de la fragilidad social, de la mortalidad y del deterioro funcional (95). Los déficits asociados a la esfera social no deben considerarse por separado de las alteraciones fisiológicas, sino que deben entenderse como una acumulación de deficiencias que también provocan cambios a nivel celular y tisular. Concretamente, la soledad puede contribuir a alteraciones en la función celular, aumentando la resistencia vascular (96) y la incidencia de enfermedades específicas como la depresión (97), el deterioro cognitivo (98), la obesidad (98), los accidentes cerebrovasculares (98) o la hipertensión (98). Los mecanismos fisiológicos que unen estas entidades radicarían en el aumento de la actividad inflamatoria, los cambios en el sistema inmunitario y neuromuscular y la influencia, a su vez, de factores sociales como el nivel socioeconómico, el nivel educativo, haber sufrido abuso o maltrato, tener pareja, o lazos familiares etc. (99).

Inactividad física y Comportamiento Sedentario

Tanto la falta de actividad física, como el comportamiento sedentario son factores de riesgo importante en el desarrollo del síndrome de fragilidad (100,101). Los estudios han demostrado que la inactividad física, definida como la realización de menos de 150 minutos de actividad de intensidad-moderada por semana, conduce a la pérdida de masa muscular y ósea, a la disminución de la capacidad funcional y al aumento de la vulnerabilidad a enfermedades crónicas, como la diabetes y las enfermedades cardiovasculares. Además, la falta de actividad física se relaciona con una mayor probabilidad de sufrir depresión y deterioro cognitivo (100).

Por su parte, el comportamiento sedentario, definido como el tiempo dedicado a actividades que se realizan estando sentado o tumbado (es decir, actividades que implican un gasto energético de entre 1,0 y 1,5 unidades metabólicas equivalentes [MeT]), también se ha relacionado con el síndrome de fragilidad en los adultos mayores, incluso en aquellos que ya cumplen con las recomendaciones de actividad física (101).

La asociación entre fragilidad y la combinación de un nivel de actividad física insuficiente y un tiempo excesivo de comportamiento sedentario puede explicarse, en buena parte, por la acumulación de efectos perjudiciales causados por estos comportamientos (102). Estos dos aspectos conductuales distintos, cuando se combinan, pueden exacerbar las alteraciones fisiológicas resultantes del propio proceso de envejecimiento provocando, entre otras, una disminución del gasto energético total, del consumo máximo de oxígeno y de la tasa metabólica en reposo (102). Además, estos comportamientos conducen a una sobrecarga calórica y a la acumulación de adipocitos centrales que, a su vez, se relacionan con la producción de adipoquinas[26] proinflamatorias, contribuyendo a la inflamación crónica de bajo grado. Así pues, esta cascada de procesos puede terminar dando lugar al desarrollo de enfermedades crónicas, factores adversos para la salud y, en consecuencia, fragilidad en los adultos mayores (102).

Sarcopenia

La sarcopenia es uno de los determinantes más relevantes del desarrollo del síndrome de fragilidad. En este sentido, debido a la importancia que adquiere esta condición en la presente tesis doctoral, se va a proceder a desarrollarla en una sección propia.

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[26] Citocinas liberadas por el tejido adiposo. De manera análoga a las mioquinas, tienen diferentes efectos a nivel autocrino, paracrino o endocrino.

SARCOPENIA

En la presente sección se detallarán los aspectos más relevantes de la sarcopenia. Se comenzarán describiendo los antecedentes y la definición de esta patología, se continuará con su fisiopatología, y se terminará explicando dos entidades específicas, ambas relacionadas con la sarcopenia, como son la obesidad sarcopénica y la osteosarcopenia.

Definición y Antecedentes

La sarcopenia es la base biológica del fenotipo de fragilidad (39). El nombre sarcopenia deriva del griego, de las palabras "sarx", que significa carne o cuerpo, y "penia", que significa pérdida (39). Se describió por primera vez en la década de 1980 como una disminución de la masa corporal magra relacionada con la edad que afecta a la movilidad, al estado nutricional y a la independencia (103). Actualmente, la sarcopenia es una enfermedad en el músculo esquelético caracterizada por una pérdida excesiva de masa muscular (cantidad de músculo) y fuerza (función muscular) con la edad, lo que a su vez se asocia con una mayor probabilidad de sufrir discapacidad física, mortalidad, importantes costes de atención médica y una pérdida significativa de calidad de vida (104). Además, la sarcopenia puede ser clasificada como "primaria" o "secundaria" (105). La sarcopenia primaria, también conocida como sarcopenia relacionada con la edad, ocurre cuando no se evidencia otra causa específica (105). Por otro lado, la sarcopenia secundaria puede ser provocada por factores causales adicionales a la edad, como enfermedades sistémicas que provocan procesos inflamatorios, como cáncer o falla de órganos (105).

Aunque desde 2016 se reconoce la sarcopenia como una condición definida según la Clasificación Internacional de Enfermedades en su 10ª edición (ICD-10-CM código M62.84) (106), a día de hoy no existe un consenso sobre cómo diagnosticarla. En este sentido, se han propuesto diversos algoritmos para definirla (107,108). En 2010, el *European Working Group on Sarcopenia in Older People* (EWGSOP) la definió como baja masa magra y baja fuerza o función (109). En una posterior revisión en 2019, EWGSOP2 considera la fuerza como el componente principal de la sarcopenia y define la "sarcopenia probable" como baja fuerza, la "sarcopenia confirmada" como baja fuerza y baja masa magra y la "sarcopenia grave" como baja fuerza, baja masa magra y desempeño físico deteriorado (105). Durante esos mismos años, otros grupos han realizado diferentes consensos sobre la sarcopenia, como *International Working Group on Sarcopenia* (IWGS) en 2011 (110). Por su parte, el Proyecto de Sarcopenia de la Foundation for the National Institutes of Health (FNIH), definió en 2014 la sarcopenia como debilidad en la fuerza de agarre y baja masa magra apendicular ajustada por índice de masa corporal (111). Ese mismo año, en Asia, varias naciones realizaron su propio consenso sobre sarcopenia, con su propio diagrama de cribado y diagnóstico bajo el nombre *Asian Working Group on Sarcopenia* (AWGS) (112). Al igual que el grupo europeo, en 2019 realizaron una nueva actualización del consenso (AWGS2) (113), modificando los puntos de corte ya establecidos en 2014. En 2020, el Consorcio de Definiciones y Resultados de Sarcopenia (SDOC, del inglés *Sarcopenia Definitions and Outcomes Consortium*) propuso una versión actualizada de la definición en términos de debilidad de agarre y velocidad de marcha lenta (114). En 2021, varios países asiáticos publicaron su consenso bajo el nombre de *South Asian Working Action Group on SARCOpenia* (SWAG-SARCO) (115). Finalmente, la *Australian and New Zealand Society for Sarcopenia and Frailty Research* (ANZSSFR) publicó su propio consenso y diagnóstico en 2022 (116).

La prevalencia de la sarcopenia depende en gran medida de los parámetros utilizados para su diagnóstico clínico, lo que la convierte en una medida algo subjetiva (117–119). Se estima que la prevalencia global de la sarcopenia es de aproximadamente entre el 6-22% en adultos de 65 años o más, con una variación según los entornos sanitarios y aumentando también con la edad (120,121). En España, un estudio realizado en 200 adultos mayores sanos, residentes en un área urbana, reportó una prevalencia de sarcopenia del 10% en hombres y del 33% en mujeres (122).

A pesar de compartir características fenotípicas similares, la sarcopenia y la fragilidad son conceptos diferentes (79). Como ya se ha comentado, la sarcopenia es una enfermedad del tejido muscular, mientras que la fragilidad es un síndrome geriátrico, de carácter multidimensional y que abarca a su vez diferentes cuadros clínicos (105). En este sentido, la mayoría de las personas frágiles son sarcopénicas, y a su vez, algunos adultos mayores con sarcopenia también son frágiles. Al igual que en la fragilidad, el bajo desempeño físico es una característica distintiva de la sarcopenia (105). Sin embargo, el síndrome de fragilidad incluye otros impedimentos, como la pérdida de peso no intencional, el agotamiento, la debilidad y afecta en gran medida el estado cognitivo, la participación social y otras circunstancias ambientales (117). Por su parte, a diferencia de la caquexia[27], la pérdida de masa muscular relacionada con la sarcopenia no necesariamente se acompaña de una disminución en el peso corporal (123). En su lugar, la sarcopenia típicamente no muestra cambios en el peso corporal general, pero la proporción de grasa respecto a músculo aumenta (117). Esta entidad patológica, conocida como “obesidad sarcopénica", muestra alteraciones en la composición muscular, resultado de la infiltración de grasa en el músculo (117). A su vez, esta tendencia se agrava aún más con la edad, ya que la deposición de grasa se desplaza de la grasa subcutánea, mientras que los depósitos de grasa intramuscular y visceral aumentan. El consecuente cambio en la calidad de la masa muscular afecta la función muscular y eleva el riesgo de mortalidad del paciente (117).

Fisiopatología

El músculo esquelético es el órgano más grande del cuerpo (124). Los músculos esqueléticos se caracterizan principalmente por su actividad mecánica requerida para el mantenimiento de la postura, el movimiento y la respiración, que dependen de las contracciones de las fibras musculares (124). Sin embargo, el músculo esquelético no es solo un componente de nuestro sistema locomotor (125). Ya en 2013, Pedersen y colaboradores propusieron denominar "mioquinas"[28] a las citoquinas que son producidas, expresadas y liberadas por las fibras musculares; y

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[27] Enfermedad sistémica caracterizada por una pérdida de peso corporal y masa muscular, acompañada de debilidad, que puede ocurre como consecuencia de otra patología crónica, especialmente el cáncer.

[28] Citocinas liberadas por las células musculares al medio extracelular en respuesta a las contracciones musculares. Tienen diferentes efectos a nivel autocrino (cuando el efecto tiene como diana la propia célula), paracrino (cuando son liberadas al líquido intersticial para actuar sobre las células vecinas) o endocrino (cuando viajan a través del torrente sanguíneo para actuar sobre células, tejidos u órganos distales)

que ejercen efectos autocrinos, paracrinos o endocrinos (124). Así pues, el secretoma muscular consiste en varios cientos de péptidos. Este hallazgo proporcionó una base conceptual y un nuevo paradigma para entender cómo los músculos se comunican con otros órganos como el tejido adiposo, el hígado, el páncreas, los huesos y el cerebro (124).

El desarrollo de la sarcopenia parece estar relacionado con una variedad de factores relacionados con el envejecimiento (28). Al igual que en el caso del síndrome de fragilidad, se considera que la inflamación crónica de bajo grado ("inflammaging") es la principal responsable del desarrollo de la sarcopenia (79). Este tipo de inflamación podría aumentarse con la liberación de citoquinas por células tumorales o de condiciones prooxidantes (79). Además, el estado proinflamatorio podría generar un aumento de la permeabilidad del intestino, dando lugar a la invasión de la microbiota intestinal en el torrente sanguíneo y desencadenando una respuesta inflamatoria sistémica mediada por la liberación de lipopolisacáridos y toxinas bacterianas (22,117).

Por otra parte, las hormonas anabólicas, especialmente la testosterona, muestran una disminución del 1% por año a partir de los 30 años (26). Esta disminución está estrechamente relacionada tanto con la pérdida muscular como con la fuerza (26). La disminución de la hormona del crecimiento conduce a una disminución del factor de crecimiento similar a la insulina-1 y del factor de crecimiento mecánico (126). Esta disminución está relacionada con la pérdida de masa muscular, pero no necesariamente con la potencia muscular. Finalmente, la disfunción mitocondrial asociada con el envejecimiento conduce no solo al daño oxidativo del músculo, sino también a una reducción en la capacidad de generar energía para permitir que los músculos funcionen correctamente (127).

La *Figura 6* recoge los principales los determinantes en la aparición de la sarcopenia explicados anteriormente.

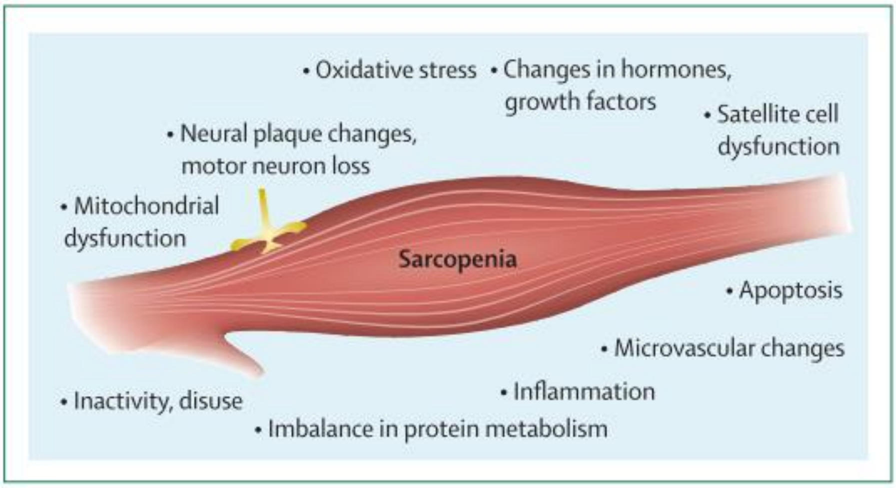

Figura 6: Determinantes de la Sarcopenia. Adaptado de Cruz-Jentoft et al. 2019 (103)

Todas estas alteraciones fisiológicas relacionadas con la edad pueden dar lugar al fenotipo de la sarcopenia, a partir de diferentes cambios en la composición y la estructura del músculo esquelético (117). En la sarcopenia se produce una disminución importante en la masa muscular, debido principalmente a la disminución en el número de fibras musculares, especialmente las fibras de tipo II (117). Esta disminución se produce de manera fisiológica durante el envejecimiento, pero en la sarcopenia lo hace de manera más pronunciada. Igualmente, tal y como se reflejó en el apartado de fisiología del envejecimiento de la presente tesis doctoral, la disminución de la expresión de los genes para la isoforma de la cadena pesada de miosina MHC2a y MHC2x se ha relacionado con la pérdida específica de las fibras musculares de tipo II en la sarcopenia (117). La debilidad muscular asociada a la sarcopenia también puede ser consecuencia de la atrofia preferencial de las fibras de tipo II (117). Además, el envejecimiento se asocia con una disminución en el número de unidades motoras que, sumado a la disminución en la capacidad de reinervación, podría contribuir a la pérdida muscular relacionada con la edad (117). Por último, las células satélite, imprescindibles para el crecimiento y la regeneración muscular después de una lesión o enfermedad, también disminuyen en número y capacidad regenerativa con el envejecimiento (126). Este decremento se observa especialmente en células satélite asociadas con fibras musculares tipo II, lo que correlaciona con la pérdida de estas fibras musculares con el envejecimiento (126).

Obesidad Sarcopénica

La obesidad sarcopénica es una condición clínica y funcional caracterizada por la coexistencia de obesidad, caracterizada por un exceso de masa grasa, y sarcopenia (128). La obesidad puede provocar pérdida de masa muscular y función debido al impacto negativo de los trastornos metabólicos dependientes del tejido adiposo, como el estrés oxidativo, la inflamación y la resistencia a la insulina, que afectan negativamente la masa muscular (129,130). Además, las personas con obesidad tienen una alta prevalencia de enfermedades crónicas no transmisibles que afectan negativamente el metabolismo muscular (131). Un estilo de vida sedentario también puede ser causa y consecuencia tanto de la sarcopenia como de la obesidad, lo que a su vez podría empeorar con enfermedades concomitantes (132). Por otro lado, la sarcopenia puede facilitar directamente la acumulación de grasa a través de la reducción del gasto energético total, y la obesidad y la sarcopenia pueden, por lo tanto, potenciar sinérgicamente una a la otra con un círculo vicioso de ganancia de grasa y pérdida muscular a través de la reducción de la movilidad, la dependencia y la discapacidad (128). Desde un punto de vista clínico, la obesidad sarcopénica conduce potencialmente a un riesgo acumulativo derivado de las dos situaciones clínicas individuales (132). Además, la interacción entre el tejido adiposo, el músculo esquelético y el hueso sustenta la idea de la importancia que tienen las estructuras tisulares en alteraciones fisiopatológicas (128). De hecho, considerar la obesidad sarcopénica como un factor de riesgo para fracturas puede parecer a priori contradictorio, ya que históricamente se ha considerado que la obesidad tiene un efecto protector contra las fracturas al aumentar la carga mecánica (133). Sin embargo, cada vez más se reconoce que la relación entre la grasa y el hueso es mucho más compleja que el simple soporte de peso (133). La infiltración de grasa en el músculo, conduce a disfunción muscular, pudiendo aumentar el riesgo de fractura (133). En general, y considerando que las fracturas de fragilidad se consideran parte de un síndrome más amplio que involucra hueso, músculo y grasa, se ha propuesto el término "síndrome de dismovilidad" como un enfoque para mejorar la identificación y el tratamiento de adultos mayores y reducir su riesgo de caídas y fracturas (133). Este enfoque es análogo al "síndrome metabólico" ampliamente reconocido en el que varias afecciones (como hipertensión, hiperlipidemia, etc.) se agrupan para mejorar su identificación y tratamiento (133).

Osteosarcopenia

Hasta hace unas décadas se asumía que la única interacción entre el músculo y el hueso era mecánica, es decir, que el músculo actuaba como una polea y el hueso como una palanca para mover al organismo (134). Como se ha reflejado anteriormente, un descubrimiento más reciente fue que el músculo, especialmente al contraerse, actúa como un órgano secretor que regula el metabolismo a través de la liberación de mioquinas. Un concepto aún más reciente es que el hueso, concretamente los osteocitos, actúan como células secretoras de las denominadas "osteoquinas", que pueden ejercer una acción autocrina, paracrina o endocrina (134,135). Así pues, el hueso y el músculo son tejidos interconectados; no sólo por la naturaleza adyacente de sus superficies, sino también química y metabólicamente. Existe una creciente cantidad de evidencia que demuestra la coexistencia de osteoporosis y sarcopenia (136–140). Aunque la sarcopenia (definida como la disminución de la masa muscular, la fuerza y la función relacionada con la edad) y la osteoporosis (que también podría definirse como la disminución de la masa ósea y la fuerza relacionada con la edad) se consideran generalmente como procesos separados, sus fenotipos se identifican cada vez más como concomitantes con el envejecimiento (141,142). Estos síndromes pueden causar un impacto dual y aumentar el riesgo de caídas, fracturas y fragilidad, con un aumento concomitante de la morbilidad y mortalidad (143). De hecho, algunos autores sugieren que la osteoporosis y la sarcopenia son el resultado de los mismos procesos que se reflejan en el hueso y el músculo, respectivamente (144). Tanto los osteoblastos como los miocitos comparten un mismo origen embriológico, que son las células madre mesenquimales (MSC) (133). Por lo tanto, se cree que la patogenicidad[29] de las MSC puede ser clave en estos trastornos, especialmente en el contexto de la senescencia celular fisiológica y la lipotoxicidad[30] (133). Con el envejecimiento, la homeostasis de las MSC se altera, lo que causa una disminución en la capacidad de renovación y diferenciación, con una disminución en el potencial osteoblástogénico y mioblastogénico a favor de una mayor adipogénesis (133). Además, muchos factores también tienen la capacidad de alterar los microambientes de las MSC y sus células hijas, como la inflamación crónica de bajo grado o los

[29] Capacidad para producir un daño celular o enfermedad.
[30] Efecto nocivo provocado por una acumulación excesiva de ácidos grasos en el interior de la célula, que provocan muerte celular o disfunción orgánica.

cambios en la concentración de adipocinas, lo que alteran aún más la homeostasis de las mismas, y que resulta en la pérdida tanto de masa ósea como muscular (133).

FUNCIÓN NEUROMUSCULAR

La función neuromuscular hace referencia a la acción coordinada entre los sistemas muscular y nervioso para producir un trabajo mecánico (145). Los determinantes más importantes de este sistema, incluirían la función muscular, cantidad muscular y la calidad muscular. Además, la función coordinada de estos sistemas en las tareas de locomoción se refleja mediante el desempeño físico (146).

En las secciones previas se han revisado los cambios que se producen a nivel fisiológico durante el envejecimiento, y durante condiciones patológicas (como la fragilidad y la sarcopenia). En el presente apartado se van a describir las herramientas de evaluación de los diferentes determinantes relacionados con el sistema neuro-musculoesquelético más utilizados tanto en el ámbito clínico como en la investigación.

En la actualidad, dentro del proceso de evaluación del estado de salud del adulto mayor, cada vez está cobrando más relevancia el análisis del desempeño físico, la función muscular, la cantidad y calidad muscular. Todos estos factores afectan a la capacidad funcional y a la independencia de los adultos mayores (146). Además, su déficit se relaciona con un mayor riesgo de sufrir eventos adversos, como caídas, fracturas, hospitalización, discapacidad, dependencia o incluso la muerte (147–150). Por último, la valoración objetiva de estos factores permite una mejor compresión, y posibilita la monitorización y la intervención temprana sobre entidades como la fragilidad y la sarcopenia de manera individualizada (151). A la hora de elegir una herramienta de evaluación, deben tenerse en cuenta la finalidad de la misma, las características de la población y la disponibilidad o no de puntos de corte para eventos adversos (151). Además, se deben considerar la aplicabilidad de las herramientas en la práctica clínica, el tiempo necesario para la prueba, el equipo requerido, las dificultad de uso de la herramienta o su coste (151). Para comenzar esta sección se tratará de definir cada uno de estos factores, y abordar sus diferentes herramientas de valoración:

Función Muscular

La función muscular se destaca por tres conceptos clave: fuerza muscular, potencia muscular y resistencia muscular (152). La fuerza muscular hace referencia a la cantidad de tensión que un músculo es capaz de producir, generalmente en un esfuerzo máximo (152). Es importante distinguir la fuerza muscular de la potencia muscular, la cual se define como la habilidad para generar la máxima fuerza en el menor tiempo posible, por ejemplo, al acelerar, saltar o lanzar objetos (152). La resistencia muscular, en cambio, se refiere a la capacidad de los músculos para generar tensión contra una carga durante un periodo prolongado de tiempo (153).

Fuerza Muscular

La fuerza muscular es una medida de la capacidad de un músculo para generar tensión contra una carga, y se expresa en Newton (N) o en kilogramos (kg) (153). A pesar de que existen pocas técnicas validadas para medir la fuerza muscular de manera adecuada en el adulto mayor, se puede evaluar tanto la fuerza de las extremidades superiores como la de las inferiores, y se ha demostrado que ambas están altamente correlacionadas (154,155). Para la evaluación de la fuerza muscular global en entornos clínicos y para el diagnóstico de sarcopenia y fragilidad, la fuerza de agarre es la medida de elección debido a que es un sustituto de la fuerza muscular de las extremidades inferiores más fácil de medir (155). La medición de la fuerza de agarre solo requiere sostener un dinamómetro de mano, tiene protocolos de medición estandarizados y dispone de valores de corte robustos y validados (156–158). Diferentes estudios indican que la fuerza de prensión manual es un indicador útil para el estado de salud general y específicamente para la mortalidad cardiovascular y para todas las causas tempranas, así como para la discapacidad (159–161). Otra medida de la fuerza muscular utilizada principalmente en el ámbito de la investigación es la fuerza isométrica de extensión de piernas (153).

Potencia Muscular

La potencia muscular es una medida que combina la fuerza y la velocidad con la que se genera dicha fuerza, expresada en vatios (W) (152). Así pues, en contraste con la fuerza muscular, la potencia se refiere al ritmo de trabajo (trabajo realizado por unidad de tiempo) (153). En las personas mayores sanas, la potencia muscular disminuye antes y más rápido que la masa y la fuerza muscular, siendo un determinante clave del desempeño físico (27). Es por esto, que la potencia muscular es a menudo el objetivo principal en las intervenciones de entrenamiento de fuerza en adultos mayores (162–164). Para medir la potencia muscular, se utilizan comúnmente ejercicios de prensa de piernas y extensión de rodilla que requieren máquinas complejas y a veces costosas, así como un tiempo y una formación considerables (153). Además, no existen protocolos estandarizados disponibles ni puntos de corte acordados para definir una potencia muscular baja, lo que limita la utilidad de la evaluación de la potencia muscular en la práctica diaria, aunque su aplicabilidad en entornos clínicos es prometedora (165). En los últimos años se vienen desarrollando herramientas más sencillas y asequibles para valorar la potencia muscular tanto en el ámbito clínico como en investigación. De entre ellas destacan los *encoder lineales*, en los que una resistencia se opone al movimiento de una articulación, permitiendo calcular la "velocidad de movimiento máximo", que se define como la máxima velocidad que un individuo puede generar al mover una carga determinada (166). Uno de los movimientos más utilizados para medir la potencia muscular mediante el encoder es el de levantarse de la silla lo más rápido posible (166–168). Además, a partir del tiempo del ejecución del test de sentarse y levantarse de la silla, y teniendo en cuenta las características antropométricas de la persona, se han validado fórmulas que permiten calcular la potencia muscular (169,170).

Cantidad Muscular

Tanto en el ámbito clínico como en el de investigación se utilizan enfoques diferentes para evaluar la cantidad de masa muscular (152). Por ello, cuando se describen medidas de masa o tamaño muscular, es imprescindible reflejar de manera coherente y precisa la métrica y el método utilizados para la aproximación (por ejemplo, "masa magra DXA" o "CSA CT") (121,152,171).

Los *golden standards* para la evaluación no invasiva de la cantidad o masa muscular son la resonancia magnética (MRI) y la tomografía computarizada (CT), pero estas herramientas no son comúnmente utilizadas en atención primaria debido a los altos costes de los equipos, la falta de portabilidad y la necesidad de personal capacitado para usar los equipos (121,152). La absorciometría de rayos X de doble energía

(DXA) es más accesible y proporciona una estimación reproducible de la masa de tejido magro total del cuerpo o la masa de músculo esquelético apendicular en pocos minutos, sin embargo, su elevado coste no la hace accesible en la mayoría de entornos clínicos (151). El análisis de impedancia bioeléctrica (BIA) (conocido habitualmente por la marca comercial Tanita®) se ha explorado como una alternativa para la estimación de la masa de músculo esquelético total o apendicular, aunque no mide directamente la masa muscular, sino que deriva una estimación de la masa muscular basada en la conductividad eléctrica de todo el cuerpo (107). El equipo de BIA es más asequible, ampliamente disponible y portátil, aunque las estimaciones de la masa muscular difieren cuando se utilizan diferentes marcas de instrumentos y poblaciones de referencia (152,172). Los modelos de predicción de BIA son más relevantes para las poblaciones en las que se han desarrollado, y se debe tener en cuenta la edad, la etnia y otras características de dichas poblaciones y los pacientes en la clínica (152). Además, las mediciones de BIA también pueden resultar influenciadas por el estado de hidratación del paciente (152). Asimismo, la ecografía es otra técnica utilizada para evaluar y detectar cambios en el grosor del músculo, el área transversal y el ángulo de penación en un período de tiempo relativamente corto, convirtiéndola en una herramienta con un amplio potencial futuro (152).

De entre las diferentes medidas de estimación de la masa muscular, destacan la cantidad de masa magra (de cuerpo entero o apendicular), la masa libre de grasa, el área de sección transversal muscular (CSA) o volumen muscular (120). Otros marcadores, como la circunferencia de la pantorrilla se utilizan como medidas subrogadas de la masa muscular de la pantorrilla en los instrumentos de diagnóstico de sarcopenia en entornos donde no se dispone de otras herramientas diagnósticas (120).

Calidad Muscular

La calidad muscular es un concepto reciente, más ambiguo, y que abarca las características tanto a nivel microscópico como macroscópico de la estructura y composición muscular, así como la función que brinda cada unidad de masa muscular (105). Tal y como concluye la EWGSOP en su nueva revisión sobre el diagnóstico y el manejo de la sarcopenia, hasta la fecha, no existe un acuerdo universal sobre los métodos para evaluar la calidad muscular en la práctica clínica diaria. En adelante, se espera que las evaluaciones de la calidad muscular sirvan para orientar las alternativas terapéuticas y para supervisar la respuesta al tratamiento (105). Actualmente, solo hay unos pocos métodos disponibles para evaluar de forma no invasiva la calidad muscular. De entre ellos, en la presente tesis se van a destacar la tensiomiografía (TMG) y la myotonometría (MMT) (173).

Tensiomiografía

La tensiomiografía (TMG) es un método de valoración de la función muscular válido y fiable (174,175), que se utiliza para evaluar el tono muscular. Mediante la colocación de dos electrodos en la parte más prominente del vientre muscular se genera una electroestimulación que varía en una amplitud de entre 20 a 100mA. Como resultado de la contracción muscular, se genera una disminución de su sección longitudinal, lo que a su vez genera un aumento de su área de la sección transversal. Este aumento de la sección transversal se visualiza mediante un desplazamiento en dirección radial, es decir, perpendicular al vientre del músculo. A partir de ese desplazamiento, se establecen diferentes variables, entre las que destacan, por ser las más consistentes, el *máximo desplazamiento radial* (Dm) y el *tiempo de contracción* (Tc) (176). El resto de variables obtenidas son el *tiempo de latencia* (Td), el *tiempo de mantenimiento de la contracción* (Ts) y *tiempo de relajación* (Tr) (177).

La *Figura 7* representa la gráfica de desplazamiento-tiempo que se genera con la tensiomiografía. Como puede observarse, el incremento desde el valor basal hasta el máximo punto de desplazamiento corresponde al Dm. A partir de este máximo desplazamiento, y teniendo en cuenta el tiempo transcurrido hasta llegar a este, se define la variable Tc. Cada músculo tiene su propia gráfica característica, que podrá variar según las condiciones en las que se encuentre ese músculo (177).

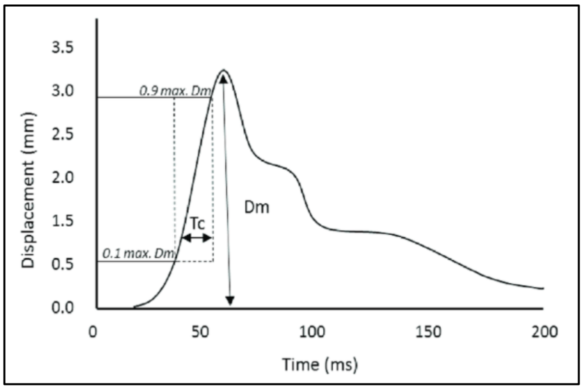

Figura 7: Tensiomiografía. Curva Desplazamiento-Tiempo. Adaptado de Macgregor et al. 2018 (178)

El Dm refleja el máximo desplazamiento radial, medido en milímetros, del músculo al ser sometido a una contracción involuntaria mediante electroestimulación. Valores bajos de Dm se han asociado un tono muscular alto, mientras que los valores más altos lo han hecho a un tono muscular más bajo (179). De hecho, en sujetos encamados, se ha reportado un incremento de Dm asociado a la pérdida de masa muscular (180), aunque no está claro si en la sarcopenia relacionada con la edad se producen estos cambios. Por su parte, el Tc refleja el tiempo, medido en milisegundos, que tarda la musculatura en alcanzar del 10 al 90% del máximo desplazamiento radial (Dm) (181). Valores aumentados de Tc se han relacionado con estados de fatiga muscular (182). Además, algunos estudios han correlacionado los niveles de Tc del músculo con muestras reales de biopsias musculares, concluyendo que la tensiomiografía, a partir de los valores de Tc podría ser una herramienta no invasiva de estimación del porcentaje de fibras tipo I del músculo esquelético, (183–185). De hecho, algunos estudios muestran como el Tc es más elevado en la población de adultos mayores en comparación a adultos más jóvenes (186,187), aunque estas diferencias podrían variar según el tipo de actividad física. De hecho, en atletas masters[31] de potencia (saltadores, esprintes etc.), el aumento del Tc relacionado con la edad es mucho menor que en atletas masters de deportes de resistencia (187) sugiriendo que los cambios en la composición de las fibras musculares podrían depender del tipo de actividad realizada.

Myotonometría

La myotonometría (MMT) es otro método de valoración de la función muscular que se utiliza para valorar las propiedades viscoelásticas de los tejidos (181). Para realizar la medición, es necesario que el paciente se situe de tal forma que la musculatura a evaluar se encuentre en total relajación. A continuación, se coloca el sensor del dispositivo en posición perpendicular a la parte más prominente del vientre muscular a evaluar. Desde esta posición, se ejerce una pequeña presión con el dispositivo sobre el tejido para que éste pueda realizar tres aplicaciones cortas de presión sobre el tejido (181). La MMT se realiza mediante el dispositivo MyotonPro

[31] Aquel deportista veterano, cuya edad media habitual supera a la de los deportistas de élite, que entrena o participa en competiciones deportivas. En la mayoría de deportes, esta categoría suele considerarse a partir de los 35 años, en bloques de 5 años, hasta los más de 105 años.

(MytonPro, Myoton Ltds., Estonia), ya que ha resultado ser un dispositivo válido y fiable (188–190). Las variables del tejido obtenidas mediante este dispositivo son la *frecuencia*, *rigidez* (o *stiffness*), *decremento*, *tiempo de relajación* y el *creep* (191). De entre los valores obtenidos mediante la MMT destaca el *sitffness.* Esta variable se determina por la relación entre la fuerza producida por el impulso mecánico y la profundidad de la deformación del tejido. Su unidad de medida son los newton por metro ($N\ m^{-1}$) (181). Valores altos de *stiffness* estarían relacionados con un aumento de la rigidez de los tejidos (192). En adultos mayores, se han encontrado valores más elevados de *stiffness* que en personas más jóvenes (193), aunque una vez más, estas diferencias eran menores en adultos mayores activos frente a personas sedentarias.

Desempeño Físico

El concepto de desempeño (o rendimiento) físico ha cambiado en las últimas décadas. Originalmente, se utilizaban medidas de desempeño físico para evaluar objetivamente cómo una persona realizaba diferentes actividades de la vida diaria (AVD) o tareas físicas en la clínica, en contraposición a las escalas de AVD basadas en preguntas sobre la capacidad para realizar tales tareas (153). Sin embargo, en las últimas décadas, este concepto ha evolucionado gradualmente y las medidas del desempeño físico están ahora relacionadas principalmente con la deambulación y las transferencias (153). De hecho, algunas medidas de desempeño físico, como la velocidad de la marcha, se han convertido en parte principal de las definiciones de fragilidad y sarcopenia (37,105). El desempeño físico podría definirse como "una función de todo el cuerpo medida objetivamente y relacionada con la movilidad"

(153). Este concepto va más allá de las medidas de la función muscular, ya que implica a muchos otros órganos y sistemas corporales, como los huesos, el equilibrio y otras entradas neurológicas, aspectos cardiovasculares, motivación, etc., lo que lo convierte en un concepto multidimensional (153). Por lo tanto, está vinculado al concepto de capacidad intrínseca de la OMS en sus aspectos relacionados con la locomoción (33). Como aspecto a destacar, las deficiencias en el desempeño físico pueden ser evidentes mucho antes de que comience la discapacidad, lo que permite detectar la vulnerabilidad en los primeros pasos de la cascada de discapacidad (153).

La evaluación objetiva del desempeño físico implica poner a prueba la capacidad de un individuo en un ambiente normalizado (152). Hay varias pruebas que se utilizan para medir el desempeño físico de manera objetiva, que incluyen pruebas de velocidad de marcha (tanto de corta como de larga distancia, con una longitud de 4m hasta 400m o más), pruebas de equilibrio, pruebas de levantarse de la silla de manera repetida (5 veces, o máximas repeticiones en 30 segundos), la prueba *Timed Up and Go* (TUG) o diferentes baterías de test, entre la que destaca el *Short Physical Performance Battery* (SPPB) (152). De entre ellas, en la presente tesis se van a destacar las siguientes:

- Short Physical Performance Battery (SPPB)

Se trata de una batería de test funcionales ampliamente utilizada en atención primaria y en investigación. Consta de 3 pruebas: Test de equilibrio en posición de pies juntos, semitándem (el talón de un pie junto al dedo gordo del otro) y tándem (el talón de un pie delante y tocando los dedos del otro pie) durante 10 segundos con los ojos abiertos; test de velocidad de marcha 4 metros y test de sentarse y levantarse de la silla 5 veces. Cada resultado en las tres pruebas tiene un valor numérico del 0-4 que se suma para obtener una puntuación global máxima de 12 puntos. Estudios previos han establecido el punto de corte en una puntuación de 8 puntos en la suma de las 3 pruebas, por debajo de los cuales de los cuales se considera que la persona está en riesgo de sufrir eventos negativos futuros, tales como caídas, hospitalizaciones, sarcopenia o fragilidad (194). La fiabilidad de la prueba test-retest ha demostrado ser de buena a excelente (el ICC entre 0.83-0.92 para medidas realizadas con una semana de diferencia), así como una fiabilidad inter-evaluador excelente (ICC 0,91) entre los pacientes mayores ingresados de forma aguda (153).

- Test de la marcha de 4 metros

Refleja el tiempo (en segundos) que tarda la persona en recorrer 4 metros. Queda incluido en la batería SPPB, pero su puntuación tiene valor individual por sí mismo. Habitualmente, la prueba se realiza dos veces y se escoge la que obtiene un tiempo menor. Su fiabilidad ha sido estudiada previamente (ICC=0.96, 95%CI=0.94-0.98; SEM=0.01) (195). Estudios previos han establecido el punto de corte en una velocidad inferior a 0.8m/s (lo que equivale un tiempo superior a 3.2 s en la prueba), a partir de la cual se considera que la persona está en riesgo de sufrir eventos negativos futuros, como fragilidad, sarcopenia, caídas u hospitalización (105,196).

- Five-Times Sit to Stand Test (5XSST)

Refleja el tiempo (en segundos) que tarda la persona en sentarse y levantarse cinco veces de una silla con respaldo, sin ayuda de los brazos. Queda incluida en la batería SPPB, pero su puntuación tiene valor individual por sí mismo. Habitualmente, la prueba se realiza dos veces y se escoge la que obtiene un tiempo menor. Estudios previos han establecido el punto de corte en 15 segundos, a partir de los cuales se considera que la persona está en riesgo de sufrir eventos negativos futuros, como fragilidad, sarcopenia, caídas u hospitalización (105).

- Timed Up and Go test (TUG)

Se trata de otro test utilizado comúnmente tanto en consulta como en investigación. Refleja el tiempo (en segundos) que tarda la persona en levantarse de la silla, con ayuda de los brazos, caminar 3 metros, girar alrededor de un obstáculo, volver a la silla y sentarse de nuevo. Habitualmente, se realiza la prueba dos veces y se escoge la que obtiene un tiempo menor. Estudios previos han establecido el punto de corte en 20 segundos, a partir de los cuales se considera que la persona está en riesgo de sufrir eventos negativos futuros (105). Además, su fiabilidad ha sido estudiada previamente. Su fiabilidad ha sido estudiada previamente (ICC=0.98, 95%CI=0.93-1.00; SEM=0.7).

EJERCICIO FÍSICO Y ENVEJECIMIENTO

Una vez explicadas las diferentes herramientas de evaluación, en la presente sección se va a tratar de exponer la evidencia acerca del ejercicio físico en el adulto mayor. Para comenzar, se mostrarán los diferentes efectos fisiológicos del ejercicio físico, y cómo estos se relacionan con el envejecimiento. Finalmente, se resumirán las recomendaciones de ejercicio físico en el adulto mayor, detallando los parámetros y consideraciones específicas para cada modalidad de entrenamiento.

Ejercicio físico y marcadores de envejecimiento

El daño celular acumulado a lo largo de la vida del individuo a menudo conduce a condiciones patológicas asociadas con la edad y, por lo tanto, lo hace más propenso a la muerte (8). El ejercicio físico realizado de manera regular en la población mayor juega un papel importante sobre los diferentes *marcadores del envejecimiento*, actuando a nivel multisistémico, generando en última estancia una disminución de la atrofia muscular severa, manteniendo la capacidad cardiorrespiratoria y la función cognitiva, potenciando la actividad metabólica y manteniendo (o incluso mejorando) la independencia funcional (13). A continuación, se reflejan los mecanismos fisiológicos específicos mediante los cuales el ejercicio físico influye en el proceso de envejecimiento a través de sus nueve marcadores:

Inestabilidad genómica y acortamiento de telómeros

El ejercicio físico juega un papel en el mantenimiento de la estabilidad genómica (13). Concretamente, el ejercicio aeróbico habitual se ha asociado con una mayor longitud de los telómeros de los leucocitos, lo que a su vez se relaciona con una mejor capacidad cardiorrespiratoria (expresada como VO2max), una menor incidencia de enfermedades cardiovasculares, así como una disminución en la mortalidad por todas las causas (15). Además, el ejercicio aumenta la expresión de proteínas protectoras y de reparación del ADN, a la vez que reduce las proteínas que regulan negativamente la progresión del ciclo celular (197). Aunque a nivel agudo aumenta el estrés oxidativo, los efectos crónicos del ejercicio físico incluyen una mayor actividad antioxidante y niveles inferiores de ROS, lo que protege del daño del ADN y disminuye el desgaste de los telómeros. Tanto las modalidades de ejercicio de fuerza como aeróbico estimulan la reserva de células satélite, lo que contrarresta el declive relacionado con el envejecimiento (13,197).

Adaptaciones epigenéticas

El ejercicio aeróbico regular puede modificar el genoma humano a través de la metilación del ADN (197). De esta manera, mediante el uso de mecanismos epigenéticos, el ejercicio aeróbico podría inducir la transcripción de genes que codifican proteínas estabilizadoras de los telómeros y la actividad de la telomerasa (13).

De manera aguda, el ejercicio también estaría asociado con un aumento en la expresión del ARN mensajero (ARNm), gracias a la hipometilación transitoria del ADN de regiones promotoras específicas de genes (15). Además, durante el período de recuperación, esta elevación del ARNm permite la síntesis de proteínas e induce una remodelación estructural gradual y modificaciones funcionales a largo plazo (15).

Finalmente, de manera crónica, el ejercicio aeróbico moderado podría aumentar los niveles de metilación del gen de la proteína caspasa tipo mota asociada a la apoptosis proinflamatoria, que modula la IL-18 y la IL-1b en los leucocitos envejecidos, lo que contribuye a reducir las citoquinas proinflamatorias relacionadas con la edad (15).

Pérdida de proteostasis

La actividad física estimula la autofagia en distintos tejidos del cuerpo, como el cerebro, músculo y corazón, y también regula positivamente los marcadores de autofagia en el músculo (197). El ejercicio aeróbico es capaz de activar la autofagia, lo que ayuda a prevenir la pérdida de masa y fuerza muscular, y se logra mediante la regulación de vías de señalización específicas como IGF-1, mTOR y FoxO3A (13). La eliminación de proteínas dañinas por medio de la autofagia también reduce el riesgo de enfermedades cardiovasculares y neurodegenerativas (13).

Desregulación de la detección de nutrientes

El ejercicio físico tiene múltiples efectos protectores en el organismo. Por ejemplo, el ejercicio puede proteger el eje somatotrófico sensible a la glucosa, resultando beneficioso para la salud general (197). Además, el ejercicio puede activar los sistemas de detección de nutrientes en los músculos, principalmente la vía mTOR sensible a los aminoácidos y la AMPK y SIRT sensibles a la baja energía, lo que promovería un estado anabólico muscular beneficioso (197). También, el ejercicio mejora la sensibilidad a la insulina, lo que puede ayudar a prevenir la diabetes tipo 2. Por su parte, particularmente el ejercicio de resistencia, es capaz de aumentar de forma aguda los niveles circulantes de testosterona, hormona del crecimiento (GH) e

IGF-1 (13,15). Estos efectos pueden ser mayores dependiendo de la intensidad o duración del ejercicio y de la cantidad de músculos involucrados. Sin embargo, es importante tener en cuenta que la tasa de síntesis de proteínas musculares en respuesta al ejercicio es menor en los ancianos que en las personas más jóvenes (13,15). Esto puede limitar la capacidad de los ancianos para mejorar la fuerza muscular y el tamaño de las fibras. Por lo tanto, es importante ajustar el programa de ejercicio a las necesidades y capacidades de cada individuo (13,15).

Disfunción mitocondrial

El ejercicio físico regular tiene efectos positivos en la función mitocondrial. Los individuos que practican ejercicio de resistencia presentan niveles más altos de proteínas mitocondriales, mtDNA y TFAM (197). La práctica regular de ejercicio físico mantiene una reserva de mitocondrias bioenergéticamente funcionales que contribuyen a reducir el riesgo de morbilidad y mortalidad a lo largo de la vida (197). En personas mayores, el ejercicio de fuerza favorece una disminución del daño oxidativo del ADN y de las alteraciones mitocondriales inducidas por el envejecimiento, mejorando así la capacidad oxidativa de las fibras musculares (13).

Senescencia celular

El ejercicio, principalmente el ejercicio aeróbico, puede disminuir la incidencia del cáncer y ayudar a mejorar el pronóstico del cáncer a través de varios mecanismos, incluyendo la secreción de mioquinas antitumorales, la mayor actividad de las células *natural killer*, la mejor expresión de antígenos, una menor inflamación y la prevención de la acumulación de células senescentes funcionales a través de la reducción de la expresión de los reguladores de la apoptosis (13,15).

Agotamiento de células madre

El ejercicio físico es un fuerte estímulo para la migración y proliferación de células madre hacia los tejidos dañados para su posterior regeneración. Realizado de manera regular, atenúa la disminución de la capacidad reparadora del endotelio de las células progenitoras endoteliales asociada con la edad (13,15). Además, activa las células madre mesenquimales, que son progenitores pluripotentes con una amplia variedad de potencial terapéutico y promueve la proliferación de células madre neurales, contribuyendo a mejorar la capacidad regenerativa del cerebro y a la capacidad cognitiva (13,15). Más concretamente, el ejercicio aeróbico aumenta las miofibrillas que contienen un mayor número de células satélite y también promueve la expansión de la reserva de células satélite (197). Por su parte, el entrenamiento de fuerza puede inducir la proliferación y diferenciación de las células satélite del músculo esquelético, lo que resulta en una hipertrofia de las fibras tipo II, no solo en adultos jóvenes, sino también durante el envejecimiento (13,15).

Alteración de la comunicación intercelular

Realizar ejercicio de forma regular parece tener efectos antiinflamatorios directos a través de la secreción de las mioquinas, lo que sugiere que la actividad física en sí misma puede reducir la inflamación sistémica de bajo grado (197). A través del ejercicio se liberan hormonas como epinefrina, cortisol, hormona del crecimiento y prolactina, que tienen efectos inmunomoduladores (124). Además, se cree que el ejercicio regular podría proteger contra la acumulación de grasa visceral y grasa ectópica, y por lo tanto proteger contra la inflamación sistémica (124).

Recomendaciones generales de actividad física en el adulto mayor

Las recomendaciones globales sobre actividad física para la salud realizadas por la OMS establecen que los adultos mayores de 65 años deben realizar semanalmente entre 150 a 300 minutos de actividad aeróbica de intensidad moderada o de entre 75 a 150 minutos de intensidad vigorosa (198). Además, como parte de su actividad física semanal, los adultos mayores deben realizar actividad física variada de carácter multicomponente[32] que enfatice el entrenamiento funcional del equilibrio y el entrenamiento de fuerza a intensidad moderada o mayor, que involucre a todos los grupos musculares principales, durante 3 o más días a la semana, para mejorar la capacidad funcional y prevenir caídas (197). Estas recomendaciones deberían seguirlas, en la medida de lo posible y con las adaptaciones individuales pertinentes, todos los adultos mayores independientemente de su nivel de desempeño físico (198).

Finalmente, desde hace unos años, las estrategias encaminadas a aumentar la actividad física a nivel poblacional y optimizar su adherencia se han centrado en promover el ejercicio a través de su integración en estilo de vida (199). Una serie de ejemplos serían subir las escaleras en lugar del ascensor, pararse sobre una pierna mientras se lavan los platos, o levantarse y sentarse lentamente sin usar los brazos. Estas actividades representarían formas de incorporar ejercicios aeróbicos, de equilibrio y de fortalecimiento, respectivamente, en las actividades cotidianas (199). Actualmente se está investigando si tales técnicas prescriptivas podrían lograr una mejor adherencia al ejercicio en comparación con los enfoques estándar para

[32] El entrenamiento de tipo multicomponente (MCT) es una modalidad de entrenamiento que incluye la combinación de al menos tres modalidades de entrenamiento entre las que destacan el entrenamiento de fuerza, potencia, aeróbico, equilibrio, entrenamiento funcional o reeducación de la marcha.

promover el cambio de comportamiento y apuntar a resultados clínicos a medio y largo plazo, como la reducción de caídas (199).

Entrenamiento aeróbico

El entrenamiento aeróbico (AT) puede contrarrestar estos efectos propios de la edad al fomentar adaptaciones en el cuerpo que mejoran tanto el consumo máximo de oxígeno (VO2max) como la capacidad del músculo esquelético para generar energía a través del metabolismo oxidativo. Estas adaptaciones se producen tanto a nivel central como en periférico (199).

Por lo general, se pueden iniciar el AT con una duración de 5 a 10 minutos durante las primeras semanas de entrenamiento, aumentando progresivamente a 15 a 30 minutos durante el resto del programa. Se pueden realizar con frecuencias de 3 a 7 días por semana, y no es necesario descansar un día entre sesiones. También se pueden dividir las sesiones en segmentos más cortos durante el día sin afectar a los beneficios del ejercicio (199). Se ha demostrado que los mayores beneficios en la capacidad aeróbica y la salud en general se logran con ejercicio aeróbico de intensidad moderada a vigorosa (MICT), y se han observado algunos resultados positivos con el entrenamiento de intervalos de alta intensidad (HIIT) en intervalos de 1 a 4 minutos con una frecuencia cardíaca máxima del 85 al 95% (200). En algunos adultos mayores, la frecuencia cardíaca no es un indicador confiable de la intensidad del ejercicio debido a condiciones médicas como la fibrilación auricular, los marcapasos o los betabloqueantes, por lo tanto, es necesario utilizar otros métodos para controlar la intensidad del ejercicio, como las escalas de calificación del esfuerzo percibido, donde las intensidades de 12 a 14/20 en la escala de Borg parecen ser adecuadas para el ejercicio aeróbico de intensidad moderada (199).

Existen diversas opciones de ejercicios aeróbicos que pueden ser realizados por adultos mayores, incluyendo caminar con cambios de ritmo y dirección, caminar en tapiz rodante, subir y bajar escaleras, en cicloergómetro, cicloergómetro de manos, bailar y hacer ejercicio acuático. Es importante que la elección de la modalidad de ejercicio se base en la preferencia individual, la accesibilidad, las comorbilidades cognitivas y físicas, así como los problemas musculoesqueléticos específicos de cada persona (199). Es importante aumentar progresivamente la intensidad del ejercicio para continuar adaptándose al entrenamiento aeróbico (199). Para progresar en el AT al caminar, se pueden agregar pequeñas pesas alrededor de las muñecas, balancear los brazos, utilizar un estilo de marcha más rápido, añadir inclinaciones, colinas o escaleras, llevar una mochila o un cinturón de peso, o empujar una silla de ruedas o cochecito con alguien dentro (199). Para progresar en el cicloergómetro, se puede aumentar la velocidad de pedaleo, o añadir resistencia a los pedales. En actividades acuáticas, se puede utilizar brazadas con los brazos y las piernas, agregar equipo resistente para el agua o aumentar el ritmo (199).

Sin embargo, adultos mayores con disminuciones funcionales graves podrían no ser capaces de realizar suficiente AT para obtener beneficios significativos en su capacidad neuromuscular (199). Hannan y colaboradores (200) sugieren que la fuerza y la potencia muscular están positivamente relacionadas con la capacidad cardiorrespiratoria en adultos mayores, y que la pérdida de masa muscular explica en gran parte la disminución de la capacidad aeróbica máxima relacionada con la edad. De esta manera, se ha demostrado que el entrenamiento de fuerza puede aumentar la capacidad aeróbica en adultos mayores, incluso sin ejercicio aeróbico (201). Además, en algunas intervenciones destinadas a mejorar la capacidad aeróbica en personas mayores frágiles, se ha incluido el AT dentro de programas de MCT, combinando el AT con entrenamiento de fuerza y de equilibrio (199).

Entrenamiento de fuerza

La realización regular de entrenamiento de fuerza (RT) con una intensidad adecuada (70 a 85% de la repetición 1RM[33]) y un volumen apropiado (2 a 3 series por ejercicio) a través de la periodización, resulta en adaptaciones neuromusculares favorables tanto en adultos mayores saludables como en aquellos que presentan patologías crónicas (202). Estas adaptaciones producen mejoras funcionales en las actividades de la vida diaria, especialmente cuando se incluye también el entrenamiento de potencia (202). Además, el entrenamiento de fuerza puede mejorar el equilibrio, preservar la densidad ósea, la independencia y la vitalidad, y reducir el riesgo de enfermedades crónicas como enfermedades cardíacas, artritis, diabetes tipo 2 y osteoporosis, al tiempo que mejora el estado psicológico y la capacidad cognitivas (202).

Dado que las adaptaciones al RT son específicas del estímulo de entrenamiento (es decir, el estrés fisiológico que se ejerce sobre el cuerpo), el cual es determinado por la dosis de ejercicio, es probable que solo se logren mejoras en la fuerza muscular y el desempeño físico si se prescribe una dosis adecuada de ejercicio para cada individuo (203). La dosis del ejercicio está compuesta por una combinación de variables entre las que destacan la frecuencia, el volumen y la intensidad del ejercicio (203). Por lo tanto, comprender cómo manipular estas variables de manera efectiva es clave para maximizar el potencial del RT como tratamiento para la

[33] La repetición máxima (o 1RM) es la cantidad mayor de peso que una persona puede levantar una única repetición, manteniendo una técnica adecuada.

sarcopenia (203). A continuación, se procederá a describir las diferentes variables en la programación del RT:

Volumen: Es la suma del número total de series multiplicado por el número de repeticiones por serie (204). En los adultos mayores, en las primeras fases del entrenamiento, el número de series por ejercicio no parece ser la variable principal responsable las ganancias de fuerza (204). Se han observado resultados similares al comparar 1-3 series durante períodos de entrenamiento a corto plazo (6-12 semanas de entrenamiento) (205). Sin embargo, se ha observado una ventaja en favor de la realización de 3 series durante períodos más largos de entrenamiento (206). A su vez, el número de repeticiones está fuertemente determinado por la intensidad del ejercicio, por lo que las repeticiones más bajas pueden inducir mayores ganancias de fuerza debido a la mayor intensidad utilizada (202). Sin embargo, las repeticiones hasta el fallo no son necesarias y no promueven adaptaciones fisiológicas adicionales en adultos mayores (202). Finalmente, aumentar el volumen de ejercicio, normalmente aumentando el número de series o de repeticiones de un ejercicio, es una estrategia sencilla y eficaz para garantizar una sobrecarga progresiva y generar adaptaciones positivas a largo plazo (204).

Intensidad: Es la magnitud del estímulo que se le proporciona al músculo durante un ejercicio, habitualmente en relación la carga, o cantidad de peso con el que se ejecuta (204). De esta manera, se puede diferenciar entre carga absoluta, es decir, el peso total con el que se realiza el ejercicio (por ejemplo, una sentadilla con Xkg), o carga relativa, teniendo en cuenta lo que esa carga supone respecto a la máxima carga que el individuo podría levantar (por ejemplo, una sentadilla con el X%1RM o con un peso con el que se realice XRM) (204). A su vez, se puede diferenciar entre carga externa, teniendo en cuenta la cantidad objetiva de peso con la que se realiza el ejercicio, y carga interna teniendo en cuenta la cantidad de esfuerzo subjetivo que este peso supone para la persona (204). Los mayores incrementos en cuanto a la mejora de la fuerza se han obtenido a intensidades altas, y los incrementos han sido menores cuando las intensidades del entrenamiento son bajas (202). En este sentido, tampoco es necesario postergar la introducción del entrenamiento de alta intensidad para adultos mayores frágiles (199). Aunque al principio las cargas absolutas que se pueden levantar pueden ser muy bajas, incluso la fragilidad extrema no implica una contraindicación para el ejercicio intenso, sino todo lo contrario (199). A pesar de todo, es importante entender que calcular el 1RM directamente puede resultar complejo y requiere estar familiarizado con la técnica del ejercicio para evitar lesionarse durante el procedimiento (204). Además, la 1RM de un ejercicio no es constante, sino que varía diariamente debido a múltiples factores, y esta variabilidad es aún mayor en adultos mayores (204). Por tanto, basar la prescripción de la intensidad en el %1RM podría ser inefectivo, impreciso o ineficiente (204). En su lugar, las escalas de esfuerzo percibido (RPE) pueden proporcionar un enfoque más práctico para prescribir la intensidad (204). La evaluación inicial de la fuerza muscular puede ser útil para determinar la intensidad inicial de los ejercicios, aunque a menudo implica un enfoque de prueba y error (204). Los fisioterapeutas deben trabajar en colaboración con los pacientes para asegurarse de que estén comprometidos y participen activamente en el diseño y la evolución de su programa de ejercicios (204). La evaluación periódica de la fuerza muscular y el desempeño físico pueden ser útiles para guiar la progresión de la dosis de entrenamiento y motivar a los individuos a adherirse al programa de ejercicios (204). Con respecto a los parámetros específicos de la intensidad, es importante considerar las necesidades individuales de cada paciente (204). Los adultos mayores con sarcopenia severa o que presentan una debilidad significativa pueden obtener beneficios considerables con el RT a una intensidad más baja (por ejemplo, 30-60% de 1RM o RPE 4-6) o utilizando solo el peso corporal (204). Por otro lado, los adultos mayores con mayor fuerza y desempeño físico de base pueden necesitar una intensidad más alta (por ejemplo, 50-70% de 1RM o RPE 5-7) para lograr adaptaciones positivas (204). A medida que avanza el programa de entrenamiento, la intensidad puede progresar a un rango de 70-85% de 1RM o un RPE de 7-8 para optimizar las ganancias en fuerza muscular (202,207).

Frecuencia: Se trata del número de sesiones semanales en las que se realiza un entrenamiento para un grupo muscular/patrón de movimiento determinado (204). Los programas de RT que involucran dos sesiones de entrenamiento por semana parecen ser más beneficiosos en comparación con los que incluyen únicamente un entrenamiento por semana para mejorar la fuerza muscular (208). Sin embargo, no está claro si agregar una tercera sesión por semana proporciona un efecto mayor significativo; e incluso podría generar demasiada fatiga y sobreentrenamiento en algunos casos (208). En aquellos individuos con baja fuerza muscular inicial o sarcopenia severa, una sola sesión de RT por semana aún podría brindar un beneficio significativo y sería apropiado comenzar con una sola sesión de entrenamiento semanal antes de progresar a dos sesiones por semana con el tiempo (209). A medida que el individuo avanza en el programa de entrenamiento, aumentar el número de sesiones semanales de RT puede ser una estrategia efectiva para garantizar que se proporcione la sobrecarga adecuada (204). Finalmente, agregar ejercicios de fuerza funcionales que los adultos mayores puedan hacer en casa entre las sesiones de ejercicio programadas puede proporcionar beneficios adicionales y apoyar el cambio de comportamiento y la formación de hábitos positivos en torno a la actividad física (204).

Descanso: Los períodos de descanso dentro de una sesión se refieren al tiempo de recuperación entre series y ejercicios y están determinados en gran medida por la interacción de otras variables de entrenamiento, incluida la selección de ejercicios, la intensidad y el volumen (204). En programas de RT para adultos mayores, los períodos de descanso típicamente varían de 60 a 180 segundos entre series y de 3 a 5 min entre ejercicios (204). Aunque se desconoce cuáles son los períodos de descanso óptimos durante el RT, en las primeras etapas del programa, estos deben determinarse según la tolerancia del individuo al estímulo del ejercicio, y el fisioterapeuta debe trabajar con el individuo para garantizar que sean apropiados (204). Finalmente, se recomienda un mínimo de 48 h de descanso entre sesiones que involucren los mismos grupos musculares para permitir que los músculos se recuperen y se produzcan las adaptaciones hipertróficas al daño muscular excéntrico y la reparación. (202).

Selección de ejercicios: Es recomendable prescribir un ejercicio de tipo multiarticular para los grupos musculares principales, aunque las extremidades inferiores pueden requerir dos (202). La elección de rutinas de entrenamiento *full-body* o de grupos musculares específicos debe basarse en la situación individual de la persona y en la cantidad de tiempo disponible para el entrenamiento (202). Sin embargo, por lo general se opta por las rutinas *full-body* (202). Existen diferentes materiales que condicionarán en la selección de los ejercicios, tales como pesas libres, bandas de resistencia y máquinas de resistencia, sin embargo, la falta de equipos avanzados no debe ser vista como una barrera para la administración efectiva del RT (204). A pesar de que la selección de ejercicios es una variable con menor importancia que el volumen, la frecuencia, la intensidad y la progresión de las cargas, la elección de la modalidad de ejercicio puede influir en la naturaleza del estímulo de entrenamiento (210). Por ejemplo, las pesas libres requieren mayor actividad muscular para estabilizar y controlar el movimiento en comparación con las máquinas de resistencia (210). En la primera etapa del programa de RT o en aquellos con sarcopenia severa, es posible que se prefieran ejercicios en una silla o actividades que utilicen bandas de resistencia o el peso corporal del paciente (210). Sin embargo, los profesionales deben buscar avanzar más allá de estos modos de ejercicio tan pronto como sea seguro, ya que pueden limitar la sobrecarga progresiva del individuo (210). A medida que se desarrolla el programa de RT, se podrán prescribir ejercicios más avanzados como pesas, pesas rusas, balones medicinales o ejercicios en el suelo. Se debe dar prioridad a los ejercicios multiarticulares sobre los monoarticulares, realizando los ejercicios de mayor prioridad al comienzo de la sesión (204). Los adultos mayores con sarcopenia deben seguir un programa de RT que involucre ejercicios multiarticulares para los principales grupos musculares (204). Los ejercicios enfocados en los músculos de la parte inferior del cuerpo son fundamentales para el desarrollo de habilidades funcionales, como caminar, levantarse de una silla y subir escaleras (204). Asimismo, la fuerza muscular de la parte superior del cuerpo también es crucial para realizar actividades diarias básicas e instrumentales, como vestirse, cocinar y cuidarse a sí mismo (204). La inclusión de ejercicios que involucren el agarre puede tener un efecto positivo en la fuerza del antebrazo y del agarre, habilidades necesarias para realizar las actividades instrumentales de la vida diaria, como comer, caminar, bañarse, vestirse, trasladarse e ir al baño (204). Mejorar la fuerza del tríceps braquial en la extensión del codo también puede ser importante para levantarse de la silla y realizar transferencias (204,210).

Duración: La duración del programa de entrenamiento hace referencia a la cantidad de tiempo (generalmente medido en semanas o meses) durante el cual se desarrolla el programa de entrenamiento (204). Se necesitan al menos 12 semanas de RT para maximizar los efectos del RT (204).

Otras consideraciones: El RT realizado de manera grupal puede proporcionar un entorno de apoyo y un mayor compromiso social entre los participantes, lo que a menudo resulta en una mayor adherencia al programa de entrenamiento (204). Por otra parte, durante las sesiones, es importante educar a los adultos mayores que participan en el entrenamiento de fuerza sobre las sensaciones normales asociadas con el entrenamiento de fuerza, como la fatiga, el dolor muscular o la sensación de incomodidad que se da tras el entrenamiento, principalmente durante las primeras sesiones la respuesta normal del dolor muscular posterior al ejercicio (204).

El entrenamiento físico implica realizar sesiones repetidas y sistemáticas de ejercicio para mejorar una capacidad física o habilidad (204). La dosis de ejercicio, entendida como el estímulo del entrenamiento, es el principal determinante de la respuesta aguda y adaptación crónica al entrenamiento. Los principios de especificidad, sobrecarga y progresión son fundamentales en el diseño de intervenciones de RT que estimulen respuestas de entrenamiento positivas y logren los resultados deseados (204). La especificidad del ejercicio implica que este debe estar específicamente dirigido a inducir mejoras en el resultado deseado (204). La sobrecarga se refiere a la necesidad de que el ejercicio ejerza una tensión mayor que la habitual en el cuerpo para que se produzca la adaptación (204). La progresión del estímulo de entrenamiento es esencial para impulsar la adaptación continua y se puede lograr mediante la manipulación de variables de RT, como la intensidad, el volumen y la frecuencia (204). Además, la programación del entrenamiento habitual necesita ajustarse al nivel de fatiga, la aparición de dolor o las limitaciones funcionales transitorias que sufren los adultos mayores en su día a día (202). En este sentido, tras cada sesión de entrenamiento, se pueden emplear escalas de esfuerzo percibido (como el RPE) para decidir si aumentar la carga del entrenamiento de manera segura, manteniendo el RPE en un rango duro a muy duro (RPE 7-8) (204). Monitorizar la respuesta aguda al entrenamiento en cada sesión permitirá también al fisioterapeuta determinar si se necesita aumentar o disminuir el estímulo de entrenamiento para asegurar una sobrecarga adecuada. Las calificaciones de RPE pueden ser una herramienta útil para guiar la prescripción de ejercicios, ya que permiten a los individuos proporcionar una evaluación subjetiva de la intensidad del ejercicio y reconocer las sensaciones de esfuerzo asociadas con la intensidad deseada (204). Además, la retroalimentación cualitativa de los individuos puede proporcionar información valiosa sobre su capacidad para realizar actividades diarias y su calidad de vida (204). Al discutir estos temas, se puede fomentar la participación activa de los adultos mayores en el diseño y la entrega de su programa de ejercicios, en lugar de ser meros receptores pasivos. (204).

Seguridad y contraindicaciones: A pesar de la posible peligrosidad del entrenamiento de fuerza para los adultos mayores, una reciente revisión sistemática ha concluido que las intervenciones a largo plazo (1 año o más) no generan a problemas de salud o mortalidad en adultos mayores (211). De hecho, el RT se ha asociado con una reducción del riesgo de mortalidad en poblaciones clínicas, una reducción en el número de caídas y lesiones asociadas a caídas, y una mejora tanto en la función física como la cognitiva (211). Sin embargo, a pesar de la evidenciada seguridad del entrenamiento de fuerza en adultos mayores, la evaluación médica puede ayudar a identificar a aquellos que puedan estar en mayor riesgo debido a condiciones médicas inestables (211). Concretamente, el entrenamiento de fuerza puede tener ciertas contraindicaciones debido al riesgo de un aumento excesivo de la presión arterial durante la maniobra de Valsalva (202). Dentro de las contraindicaciones absolutas destacan condiciones como la cardiopatía coronaria inestable, insuficiencia cardíaca descompensada, arritmias no controladas, hipertensión pulmonar grave, estenosis aórtica grave y sintomática, miocarditis aguda, endocarditis o pericarditis, hipertensión no controlada, disección aórtica y síndrome de Marfan (202). También se deben evitar entrenamientos de alta intensidad en pacientes con retinopatía proliferativa activa o retinopatía diabética no proliferativa moderada o peor (202). Por su parte, las contraindicaciones relativas incluyen factores de riesgo de cardiopatía coronaria, diabetes, hipertensión no controlada, baja capacidad funcional, limitaciones musculoesqueléticas y la presencia de dispositivos médicos (202). Es importante individualizar la intensidad y la progresión del entrenamiento y considerar la experiencia de entrenamiento al establecer un programa de ejercicios (202). Los adultos mayores con discapacidades pueden requerir una mayor supervisión durante el entrenamiento de fuerza en comparación con aquellos que son más físicamente capacitados (199). Especial precaución debe tenerse durante la etapa inicial del programa, ya que una lesión menor puede requerir varias semanas de recuperación y puede provocar el abandono del programa y reforzar las creencias catastrofistas y negativas hacia el entrenamiento de fuerza (199).

Entrenamiento de potencia

El entrenamiento de potencia (PT) consiste en un tipo de entrenamiento contraresistencia realizado con cargas ligeras-moderadas y ejecutado a alta velocidad en la fase concéntrica (199). Esta modalidad de entrenamiento, que implica la aplicación de una fuerza máxima en un breve intervalo de tiempo, involucra el reclutamiento de unidades motoras de alto umbral compuestas por fibras musculares de tipo II (212). Algunos estudios concluyen que el PT podría ser más efectivo en la mejora del desempeño físico en adultos mayores en comparación con el entrenamiento de fuerza realizado a velocidades más lentas (164,213). Esto se debe a que la capacidad de realizar actividades de la vida diaria podría depender más de la capacidad de aplicar la fuerza de manera rápida que de la capacidad de ejercer una fuerza máxima (164,213). Esta modalidad de entrenamiento está asociada con una mejora en el desempeño físico y una reducción en la incidencia de caídas en poblaciones de personas frágiles y/o institucionalizadas (163,214). Por lo tanto, el entrenamiento de la fuerza muscular debe ser recomendado siempre que sea posible tanto para personas sanas como para personas mayores con sarcopenia, fragilidad y otras comorbilidades (199).

En cuanto a las recomendaciones a cerca del PT para optimizar sus beneficios, se recomienda realizarlo evitando las condiciones previas de fatiga, con un descanso suficiente entre series que asegure un mantenimiento del rendimiento, y evitando llegar al “fallo” concéntrico en las repeticiones (202). La fatiga muscular puede aumentar el riesgo de lesiones y no es necesaria para obtener respuestas adaptativas de fuerza y potencia (202). Es esencial que los ejercicios diseñados para el desarrollo de la potencia se realicen con la técnica adecuada para reducir el riesgo de lesiones, antes de progresar en carga, velocidad o intensidad (202). La fase concéntrica del ejercicio deberá realizarse lo más rápida posible (máxima velocidad intencional), seguida de una fase excéntrica más lenta y controlada (202). La potencia se maximiza con intensidades del 30-45% del 1RM para las extremidades superiores y del 60-70 % del 1RM para las extremidades inferiores (202). Si se combinan series de PT con series de RT en la misma sesión, es conveniente realizar el PT en primer lugar, para asegurar un menor estado de fatiga y un rendimiento adecuado que maximice los beneficios (202).

Finalmente, es importante destacar que se debe tener especial precaución con la ejecución de ejercicios de entrenamiento de potencia para evitar lesiones musculoesqueléticas (199). Además, se debe tener en cuenta que, en esta modalidad de entrenamiento con cargas bajas y alta velocidad, el riesgo de lesiones de meniscos o tendones puede aumentar, especialmente si existen cambios degenerativos no diagnosticados, lo que es común en adultos mayores (y todavía más frecuente si padecen osteoartritis) (199). Es fundamental que los fisioterapeutas realicen evaluaciones regulares de los pacientes antes de comenzar el entrenamiento de potencia, ya que este tipo de afectaciones pueden representar una barrera significativa para los adultos mayores que intentan realizar un entrenamiento de potencia (199).

Entrenamiento del equilibrio

En algunos adultos mayores a menudo necesitan mejorar su equilibrio antes de poder realizar adecuadamente el ejercicio aeróbico o de reentrenamiento de la marcha (199). Sin embargo, existe el riesgo potencial de sufrir caídas accidentales durante el entrenamiento de equilibrio (BT). En este sentido, una forma práctica de aplicar el BT es practicar la postura o movimiento más difícil posible en un entorno seguro sin caerse (por ejemplo, mantenerse en una pierna sin apoyo). Una vez que se domina este nivel de ejercicio, se puede avanzar al siguiente nivel más difícil, aumentando la inestabilidad o disminuyendo las aferencias visuales (ojos cerrados). Este enfoque es similar al principio de sobrecarga progresiva del RT (199). Es importante tener en cuenta que incluso en personas frágiles, el rendimiento del equilibrio puede mejorar si se realizan los ejercicios de equilibrio de manera adecuada (199). A pesar de que el BT es recomendado en los consensos de expertos para mejorar el equilibrio (199), existe cierta controversia al respecto, ya que, en poblaciones sanas, esta modalidad de entrenamiento sería eficaz para mejorar las tareas entrenadas, pero no está claro si tendría transferencia al resto de tareas no entrenadas, siendo este tipo de ejercicios “generales” poco interesantes desde un punto de vista clínico (215). En consecuencia, los fisioterapeutas deberían identificar exactamente aquellas tareas que se necesitan mejorar y utilizar estas mismas tareas tanto en el programa de entrenamiento y como parte de la batería de pruebas que evalúa la eficacia del programa de entrenamiento (215). Combinar ejercicios de equilibrio con RT, o hacerlo dentro de un programa de entrenamiento multicomponente podría ser una mejor alternativa para mejorar el equilibrio en adultos mayores (216).

Entrenamiento multicomponente

El entrenamiento de tipo multicomponente (MCT) es una modalidad de entrenamiento que incluye la combinación de al menos tres modalidades de entrenamiento entre las que destacan el entrenamiento de fuerza, potencia, aeróbico, equilibrio, entrenamiento funcional o reeducación de la marcha (199). Esta modalidad, igualmente debe seguir el principio de individualización y el de sobrecarga progresiva, incluyendo incrementos graduales de volumen, intensidad o complejidad de los ejercicios (199). El MCT parece ser la mejor estrategia para mejorar la marcha, el equilibrio y la fuerza, así como para reducir la tasa de caídas y, en consecuencia, mantener su capacidad funcional durante el envejecimiento tanto en adultos mayores sanos como en poblaciones frágiles o institucionalizadas (199).

Aunque, como ya se ha comentado previamente, las intervenciones de RT han demostrado mejoras en la función neuromuscular, los programas de MCT que incluyen RT parecen dar como resultado mayores mejoras generales, presumiblemente porque este tipo de intervención estimula varios componentes de la salud física, como la fuerza, la función cardiorrespiratoria o el equilibrio (199). Además, los programas de MCT que incluyen RT también mejoran parámetros funcionales como la marcha o el equilibrio, y reducen el riesgo de caídas (217). Finalmente, como consideraciones a tener en cuenta, el bloque de ejercicios de fuerza debe realizarse previamente al AT para maximizar sus efectos (202). Asimismo, en caso de incluir entrenamiento de potencia, debe realizarse antes que el RT para realizarlo sin fatiga y poder aprovechar al máximo sus beneficios (202).

Entrenamiento funcional

El entrenamiento funcional se enfoca en movimientos multiarticulares, complejos y dinámicos, y utiliza variaciones para mejorar la capacidad funcional para ejecutar tareas específicas de la vida diaria (199). Como ya se ha comentado en el apartado de entrenamiento de fuerza, una vez que se alcanza un cierto umbral de fuerza muscular, las mejoras adicionales en la fuerza podrían no proporcionar beneficios adicionales en el desempeño de las AVD. La disminución del desempeño físico relacionado con la edad se debe no solo a la pérdida de masa o fuerza muscular, sino también a otros aspectos esenciales del control motor, como el deterioro del equilibrio dinámico y la coordinación del movimiento (202). En este sentido, incluir ejercicios de entrenamiento funcional en un programa de entrenamiento multicomponente es beneficioso para mejorar aún más el desempeño de las AVD (202).

El entrenamiento funcional se enfoca en movimientos multiarticulares, y dinámicos, y utiliza variaciones para mejorar la capacidad funcional para ejecutar tareas específicas de la vida diaria, utilizando patrones de movimiento complejos, e incorporando múltiples aspectos del control motor para simular las actividades que resultan esenciales para la persona (202). Además, los ejercicios se pueden adaptar según las necesidades del individuo, y deben individualizarse según su capacidad y aumentar progresivamente en dificultad, ya sea aumentando la carga o el volumen, la velocidad, el rango de movimiento, agregando desequilibrios o aumentando la complejidad de la tarea (202). Algunos ejemplos de ejercicios funcionales podrían ser subir al cajón, o levantarse de la silla, el paseo del granjero etc.

A pesar de que el entrenamiento funcional se haya popularizado en los últimos años, actualmente no existen estudios que demuestren la eficacia de estos diversos métodos, y dicha comparación es difícil debido a la heterogeneidad de diseños y métodos de evaluación utilizados en los estudios de entrenamiento funcional (202). De hecho, en un artículo llevado a cabo por Ide B. y colaboradores (218) revisan la inconsistencia actual en la propia definición de entrenamiento funcional, y argumentan que las adaptaciones al ejercicio dependen del estímulo de entrenamiento específico, concluyendo que los programas y ejercicios de entrenamiento funcional no son diferentes de los que ya se prescriben mediante el entrenamiento tradicional (aeróbico, fuerza, equilibrio etc.) y que, por tanto, no habría justificación para clasificar los programas de entrenamiento físico como “funcionales”. Cualquier modalidad de entrenamiento debería programarse de acuerdo al principio de individualización, y debería prescribirse con el objetivo de mejorar las necesidades de cada persona, ya sea del rendimiento deportivo en el caso de un atleta, del desempeño físico en las AVD en el caso de un adulto mayor, o en la recuperación de un déficit neuro-musculoesquelético en el caso de existir una limitación del desempeño físico debida a alguna patología coexistente (218).

Entrenamiento con restricción de flujo sanguíneo

El entrenamiento con restricción de flujo sanguíneo (BFR-t) se conoce también con los nombres de método Kaatsu, entrenamiento oclusivo, entrenamiento hipóxico o entrenamiento torniquete. Esta modalidad utiliza una banda o un manguito neumático para restringir parcialmente el flujo sanguíneo arterial mientras se obstruye totalmente el retorno venoso. La colocación del manguito se suele combinar con entrenamiento con cargas significativamente menores (20-30% de 1-RM; 15-30 repeticiones por serie). La presión del manguito que genera la restricción del flujo varía entre 40-80% de la presión necesaria para generar una oclusión total de la extremidad, utilizando presiones más bajas en extremidades más pequeñas o en caso de molestia (219).

Actualmente, no están definidos los mecanismos fisiológicos exactos por los cuales el BFR-t genera tales ganancias en la fuerza y la masa muscular (219). Se cree que los cambios musculares se producen a través del efecto indirecto de la acumulación de metabolitos y el ambiente hipóxico, que resultan de una mayor activación muscular, fatiga y señalización anabólica que la misma intensidad de ejercicio realizado sin restricción del flujo sanguíneo (219). El papel de los metabolitos que se acumulan dentro del músculo durante el entrenamiento con restricción del flujo sanguíneo todavía no se comprende completamente (219). Algunos investigadores han sugerido que las adaptaciones musculares observadas con la restricción de flujo sanguíneo se deben a estos metabolitos, pero esta idea ha sido ampliamente debatida (219). Otras teorías sugieren que el aumento en la acumulación de metabolitos (lactato e iones de hidrógeno principalmente), y la consiguiente disminución del pH intracelular durante el BFR-t estimula ciertas fibras nerviosas, que provoca una fatiga neuromuscular temprana. Esta fatiga neuromuscular podría hacer que las unidades motoras de umbral más alto se reclutasen antes durante el BFR-t, lo que resultaría en un estímulo hipertrófico para una mayor proporción de fibras musculares que durante un ejercicio equivalente realizado sin restricción de flujo sanguíneo (219). El contexto hipóxico asociado con la restricción de flujo sanguíneo también puede inducir fatiga y promover la señalización anabólica dentro del músculo (219). La reducción severa de la disponibilidad de oxígeno durante el BFR-t contribuiría al aumento de la fatiga y a la disminución de la producción de fuerza, lo generaría un reclutamiento progresivo de unidades motoras adicionales como mecanismo compensatorio (219). Además, el aumento de la producción de especies reactivas de oxígeno como el óxido nítrico generado por las fluctuaciones en la disponibilidad de oxígeno podría estimular las células satélite musculares, favoreciendo el crecimiento muscular al activar (219). El aumento de metabolitos también contribuye a un aumento de la secreción de hormona de crecimiento y promueve una respuesta inflamatoria, lo que aumenta la producción de mioquinas, y activa de esta manera las células satélite musculares (219). Por último, se supone que este ambiente hipóxico estimula la angiogénesis a través de la proliferación del factor de crecimiento del endotelio vascular de una manera similar a la que se observa con el entrenamiento de fuerza convencional (219).

A pesar de que incluir el entrenamiento de fuerza en alta intensidad parece ser la mejor estrategia para mejorar tanto la fuerza como la masa muscular tanto en adultos jóvenes como en adultos mayores (199), existen ocasiones en que los adultos mayores no son capaces de tolerar el entrenamiento con altas cargas, ya sea por una condición musculoesquelética, como la degeneración de los tejidos articulares, la presencia de una lesión o el encamamiento (220). En estos casos, el BFR-t podría ser una buena alternativa para conseguir efectos similares a los del entrenamiento con altas cargas, pero con un menor estrés articular (25).

Como puntualización final, el uso del entrenamiento BFR-t en el entorno clínico requiere que el fisioterapeuta considere múltiples factores, como la lesión o afección médica del paciente, su historial médico, el tiempo transcurrido desde la lesión o cirugía, la elección del tipo de manguito, la presión arterial de oclusión en las extremidades, las especificaciones del ejercicio (como el número de series, repeticiones y carga) y la duración de la aplicación de BFR-t (219). Estos factores deben ser evaluados cuidadosamente para garantizar que el entrenamiento sea seguro y efectivo en cada caso específico (219). Para ampliar la información sobre cuestiones de seguridad y parámetros de aplicación, los siguientes artículos recomendados entran al detalle (219,221,222).

JUSTIFICACIÓN

La función neuromuscular en el adulto mayor es un área de investigación crucial debido a su estrecha relación con la salud y la calidad de vida en esta población. Como se ha comentado en la introducción, con el envejecimiento, se producen cambios significativos en el sistema neuromuscular, como la disminución de la masa muscular, la fuerza, la coordinación motora, así como cambios morfológicos y estructurales (cambios en el tono muscular, tiempo de activación del músculo etc.). Todos estos cambios, en última instancia, podrían tener un impacto en la pérdida de funcionalidad en los adultos mayores.

Tanto la valoración como la prescripción de ejercicio terapéutico se han convertido en dos pilares fundamentales para mejorar la función neuromuscular y promover la salud en el adulto mayor. Sin embargo, es fundamental contar con evidencia científica sólida que respalde la efectividad de los diferentes enfoques de valoración y prescripción de ejercicio terapéutico. Es en este contexto que se justifica la realización de los artículos de la presente tesis doctoral, agrupándose en dos líneas principales de investigación

La primera línea de investigación tendría como objetivo evaluar la relación entre el desempeño físico y calidad muscular. Como ya ha quedado reflejado en los apartados anteriores, el envejecimiento está caracterizado por una disminución en la calidad muscular, debido a cambios tanto estructurales como fisiológicos que se dan en el músculo esquelético y los sistemas asociados. Sin embargo, no está del todo claro que esta disminución en la calidad muscular tenga un impacto directo y proporcional en el desempeño físico. Así pues, es necesario saber qué relación existe entre estos parámetros, para seguir aumentando nuestra comprensión sobre los mismos, y mejorar el proceso de valoración musculoesquelética del adulto mayor. Además, estos estudios pueden ayudar a identificar marcadores objetivables y confiables que permitan evaluar de manera precisa y efectiva el estado de la función neuromuscular en esta población. En esta misma línea, una vez analizada la literatura acerca de la tensiomiografía y la myotonometría, se encuentran dos parámetros con fundamentos teóricos similares, uno de cada dispositivo. Se plantea estudiar si podría existir una correlación entre ellas, y por tanto, la interpretación de los resultados de un dispositivo pudieran ser extrapolados para el otro dispositivo.

La segunda línea de investigación se centra principalmente en evaluar la influencia de las diferentes intervenciones habitualmente prescritas en el adulto mayor, no sólo en la fuerza muscular, sino también en el desempeño físico. La fundamentación científica de estas intervenciones se basa principalmente en ensayos clínicos con resultados dispares, por lo que resulta primordial evaluar el efecto global reportado por los diferentes estudios, en forma de meta-análisis.

Por último, combinando las dos líneas anteriores, una vez llevados a cabo los proyectos anteriores, se plantea realizar una intervención de tipo multicomponente en una población de adultos mayores, y analizar los cambios tanto en la fuerza, como en el desempeño físico, y en los parámetros de calidad muscular.

En resumen, la realización de estos proyectos es necesaria para generar conocimiento científico que respalde la valoración y la prescripción de ejercicio terapéutico en el adulto mayor. Al proporcionar una visión integral de la evidencia disponible y analizar la relación entre los parámetros neuromusculares y el rendimiento físico, estos estudios contribuirán al desarrollo de estrategias más efectivas y personalizadas para mejorar la función neuromuscular y promover la salud en esta población.

HIPÓTESIS

Como se ha planteado en el apartado anterior, la presente doctoral tiene dos líneas de investigación diferenciadas (Líneas A y B), ambas girando en torno a la función neuromuscular en el adulto mayor.

Línea A

Hipótesis general A

La primera línea de investigación tiene como hipótesis general que existe una correlación fuerte entre las variables de fuerza muscular, desempeño físico y calidad muscular.

Hipótesis proyecto 1

Existe una fuerte correlación entre el máximo desplazamiento radial (Dm), valorado mediante TMG y el stiffness, valorado mediante MMT.

Hipótesis proyecto 2

Existe una fuerte correlación entre los test funcionales para la evaluación de la fuerza y el desempeño físico, y los dispositivos de valoración de la calidad muscular; concretamente la tensiomiografía y la myotonometría.

Hipótesis proyecto 3

Existe una fuerte correlación entre los test funcionales para la evaluación del desempeño físico, y el equilibrio estático valorado mediante estabilometría.

Línea B

Hipótesis general B

La segunda línea de investigación tiene como hipótesis general que el ejercicio físico, independientemente del tipo de modalidad, tiene efectos positivos sobre la fuerza muscular y el desempeño físico.

A partir de esta hipótesis general, se desarrollaron cuatro hipótesis específicas para los cuatro primeros artículos que componen esta tesis doctoral.

Hipótesis proyecto 4

La combinación de entrenamiento de fuerza (RT) y suplementación proteica (PS) es más efectiva que el entrenamiento de fuerza en solitario en la mejora de la fuerza y el desempeño físico en el adulto mayor sano.

Hipótesis proyecto 5

El entrenamiento con restricción de flujo sanguíneo (BFR-t) es efectivo en la mejora de la fuerza y el desempeño físico en el adulto mayor sano.

Hipótesis proyecto 6

El entrenamiento multicomponente (MCT) es efectivo en la mejora de la fuerza y el desempeño físico en el adulto mayor sano.

Hipótesis proyecto 7

Las diferentes modalidades de entrenamiento (entrenamiento aeróbico, entrenamiento de fuerza, entrenamiento de equilibrio y entrenamiento multicomponente) son efectivas en la mejora del equilibrio en el adulto mayor sano.

Teniendo en cuenta las dos líneas anteriores, se planteó un estudio de intervención.

Hipótesis proyecto 8

El entrenamiento multicomponente (MCT) es efectivo en la mejora de la fuerza, la el desempeño físico, y la calidad muscular en el adulto mayor sano.

OBJETIVOS

Objetivos proyecto 1

- Evaluar el nivel de correlación entre el máximo desplazamiento radial (Dm), valorado mediante TMG y el stiffness, valorado mediante MMT en los músculos gastrocnemios.

Objetivos proyecto 2

- Evaluar el nivel de correlación entre los test funcionales para la evaluación de la fuerza y el desempeño físico, y los dispositivos de valoración de la calidad muscular; concretamente la tensiomiografía y la myotonometría.

Específicamente:

- Evaluar el nivel de correlación entre el tiempo de contracción (Tc), valorado mediante TMG y los test funcionales de SPPB, TUG, 5XSST, velocidad de marcha en 4 metros, fuerza de agarre y fuerza de extensión de rodilla.
- Evaluar el nivel de correlación entre el máximo desplazamiento radial (Dm), valorado mediante TMG y los test funcionales de SPPB, TUG, 5XSST, velocidad de marcha en 4 metros, fuerza de agarre y fuerza de extensión de rodilla.
- Evaluar el nivel de correlación entre el stiffness, valorado mediante MMT y los test funcionales de SPPB, TUG, 5XSST, velocidad de marcha en 4 metros, fuerza de agarre y fuerza de extensión de rodilla.

Objetivos proyecto 3

- Evaluar el nivel de correlación entre los test funcionales para la evaluación del desempeño físico, y el equilibrio estático valorado mediante estabilometría.

Específicamente:

- Evaluar el nivel de correlación entre la superficie de la elipse del estabilograma, valorada con los ojos abiertos, y los test funcionales de SPPB, TUG, 5XSST y velocidad de marcha en 4 metros.
- Evaluar el nivel de correlación entre la superficie de la elipse del estabilograma, valorada con los ojos cerrados, y los test funcionales de SPPB, TUG, 5XSST y velocidad de marcha en 4 metros.
- Evaluar el nivel de correlación entre la longitud del estabilograma, valorada con los ojos abiertos, y los test funcionales de SPPB, TUG, 5XSST y velocidad de marcha en 4 metros.
- Evaluar el nivel de correlación entre la longitud del estabilograma, valorada con los ojos cerrados, y los test funcionales de SPPB, TUG, 5XSST y velocidad de marcha en 4 metros.

Objetivos proyecto 4

- Evaluar si la combinación de entrenamiento de fuerza (RT) junto con la suplementación proteica (PS) es más eficaz que el entrenamiento de fuerza solo o combinado con placebo (plS) para mejorar la fuerza muscular y el rendimiento físico en adultos mayores sanos.

Objetivos proyecto 5

- Evaluar la efectividad del BFRt en la mejora de la fuerza muscular y el desempeño físico en adultos mayores.

Objetivos proyecto 6

- Evaluar la efectividad del entrenamiento multicomponente (MCT) en la mejora de la fuerza muscular y el desempeño físico en adultos mayores.

Objetivos proyecto 7

- Evaluar que modalidad de entrenamiento (entrenamiento aeróbico, entrenamiento de fuerza, entrenamiento de equilibrio y entrenamiento multicomponente) es más efectiva en la mejora del equilibrio en el adulto mayor sano.

Objetivos proyecto 8

- Evaluar los cambios producidos por un programa MCT tanto en el desempeño físico como en la calidad muscular en una población de adultos mayores sanos.

Específicamente:

- Evaluar los cambios producidos por un programa MCT en la prueba SPPB en una población de adultos mayores sanos.
- Evaluar los cambios producidos por un programa MCT en la prueba TUG en una población de adultos mayores sanos.
- Evaluar los cambios producidos por un programa MCT en la prueba 5XSST en una población de adultos mayores sanos.
- Evaluar los cambios producidos por un programa MCT en la prueba de velocidad de marcha en 4 metros en una población de adultos mayores sanos.

- Evaluar los cambios producidos por un programa MCT en la fuerza de agarre en una población de adultos mayores sanos.
- Evaluar los cambios producidos por un programa MCT en el tiempo de contracción (Tc), valorado mediante TMG, en una población de adultos mayores sanos.
- Evaluar los cambios producidos por un programa MCT en el máximo desplazamiento radial (Dm), valorado mediante TMG, en una población de adultos mayores sanos.
- Evaluar los cambios producidos por un programa MCT en el stiffness, valorado mediante MMT, en una población de adultos mayores sanos.

METODOLOGÍA

Para responder a los objetivos planteados en los tres primeros proyectos, se llevaron a cabo 3 estudios observacionales. En el primer estudio observacional se evaluó el nivel de correlación entre las variables máximo desplazamiento radial (Dm), valorado mediante TMG y el stiffness, valorado mediante MMT. En el segundo estudio observacional se evaluó el nivel de correlación entre los test funcionales para la evaluación de la fuerza y el desempeño físico, y los dispositivos de valoración de la calidad muscular. En el tercer estudio observacional se evaluar el nivel de correlación entre los test funcionales para la evaluación del desempeño físico, y el equilibrio estático valorado mediante estabilometría.

Tras revisar la literatura actual sobre el tema, para responder a los objetivos de los proyectos 4-7, se llevaron a cabo 4 revisiones sistemáticas y meta-análisis. En la primera se evaluó la efectividad del entrenamiento de fuerza en combinación con la suplementación proteica en comparación al entrenamiento de fuerza en solitario, para la mejora de la fuerza y el desempeño físico en adultos mayores. Para las mismas variables, en la segunda se evaluó la efectividad del BFRt; y en la tercera la efectividad del MCT. En el cuarto proyecto se evaluó la efectividad diferentes modalidades de entrenamiento en la mejora del equilibrio estático.

Finalmente, para responder a los objetivos planteados en el proyecto 8, se decidió llevar a cabo un estudio de intervención de tipo cuasiexperimental, realizando una intervención mediante MCT y evaluando las variables de fuerza, desempeño físico y calidad muscular.

La metodología se encuentra detallada en cada artículo correspondiente en el siguiente apartado.

RESULTADOS

Artículo 1

Artículo 1	
Publicación	Correlation between maximal radial muscle displacement and stiffness in gastrocnemius muscle
Autores	Noé Labata-Lezaun, Carlos López-de-Celis, Luis Llurda-Almuzara, Vanessa González-Rueda, Aida Cadellans-Arróniz, Albert Pérez-Bellmunt
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Participación	Primer autor
Contribución del	Diseño del estudio, recogida de datos, análisis estadístico y redacción del artículo

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PAPER

Correlation between maximal radial muscle displacement and stiffness in gastrocnemius muscle

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Keywords: tensiomyography, neuromuscular function, myotonometry, muscle tone, stiffness

Abstract

Objective: Tensiomyography (TMG) and myotonometry (MMT) are two novel technologies that measure neuromuscular properties. These two devices measure the stiffness of the soft tissue as well as other variables. The aim of this study is to analyze if there is any correlation between *maximal radial displacement (Dm)* and *Stiffness* in the medial and lateral gastrocnemius muscles. *Approach*: An observational study was carried out in both of the limbs of 154 young adults ($n = 154$). The TMG and MMT neuromuscular response was measured in gastrocnemius medial and lateral muscles. Correlation coefficients were calculated to observe if there were any relationships between *Dm* and *Stiffness*. Differences between the dominant and the non-dominant sides and gender were assessed. *Main results*: Negative correlations between *Dm* versus *Stiffness* were found for the lateral ($r = -0.278$ and rho $= -0.248$) and medial gastrocnemius ($r = -0.207$ and rho $= -0.163$) in both dominant and non-dominant limbs respectively. *Significance*: A weak correlation between *Dm* and *Stiffness* may indicate that they assess different aspects of neuromuscular function. The MMT and TMG are independent tools, and their values cannot be extrapolated when assessing muscular stiffness. There might be some other factors that influence in this relationship; therefore, more studies are needed in order to better understand the correlation.

Correlation between maximal radial muscle displacement and stiffness in gastrocnemius muscle

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ABSTRACT

Objective: Tensiomyography (TMG) and myotonometry (MMT) are two novel technologies that measure neuromuscular proprieties. These two devices measure the stiffness of the soft tissue as well as other variables. The aim of this study is to analyze if there is any correlation between *maximal radial displacement (Dm)* and *Stiffness* in the medial and lateral gastrocnemius muscles.

Approach: An observational study was carried out in both of the limbs of a hundred and fifty-four young adults (n=154). The TMG and MMT neuromuscular response was measured in gastrocnemius medial and lateral muscles. Correlation coefficients were calculated to observe if there were any relationships between *Dm* and *Stiffness*. Differences between the dominant and the non-dominant sides and gender were assessed.

Main results: Negative correlations between *Dm* vs *Stiffness* were found for the lateral (r=-0.278 and rho=-0. 248) and medial gastrocnemius (r=-0.207 and rho=-0.163) in both dominant and non-dominant limbs respectively.

Significance: A weak correlation between *Dm* and *Stiffness* may indicate that they assess different aspects of neuromuscular function. The MMT and TMG are independent tools, and their values cannot be extrapolated when assessing muscular stiffness. There might be some other factors that influence in this relationship; therefore, more studies are needed in order to better understand the correlation.

KEYWORDS

Tensiomyography, Myotonometry, Stiffness, Muscle Tone, Neuromuscular Function.

INTRODUCTION

Neuromuscular proprieties have been widely studied during the last decades, however, there is an evident lack of consensus regarding their definitions. A clear example is that many studies include terms such as “muscle tone” or “stiffness”, often referring to similar concepts relating to neuromuscular function (NMF) (1). Some authors have distinguished one from the other, understanding that the first is obtained with the muscle at rest, while the second implies muscle contraction (2). Regardless, there is yet to be a consensus on the topic in the current literature. Additionally, the fact that there are several ways to measure neuromuscular proprieties makes it even more difficult to standardize the results and draw general conclusions.

In general, stiffness (also called “rigidity”) has traditionally been defined as the resistance of a tissue to be deformed by the application of an external force (3). Recently, two novel tools that allow the assessment of neuromuscular function and mechanical and contractile properties of soft tissues have been introduced. These techniques are tensiomyography (TMG) and myotonometry (MMT). Among their parameters, both technologies claim to be able to quantify the stiffness of tissues (4).

In TMG, *maximal radial displacement (Dm)* reflects the maximal radial displacement (in millimeters) produced by the contraction of the muscular belly (5,6). Radial displacement should vary depending on the deformation resistance of the tissue. Low *Dm* values indicate a high muscle tone (or stiffness), whereas higher values indicate a lower muscle tone (7,8).

On the other hand, in MMT, the *Stiffness* variable is determined by the ratio between the force produced by the mechanical impulse and the depth of tissue deformation [N/m] (9); and it reflects the ability of the muscle to resist changes in its shape (2). High values of *Stiffness* are related to an increase of muscle tone or tissue stiffness (10).

In this way, conceptually both *Dm* and *Stiffness* parameters seem to be related to the deformation caused by a muscle contraction stimulus. Therefore, it is likely to think that there should be a negative correlation between them.

Several studies have compared the inter-reliability and the test-retest reliability of both technologies separately (4,9,11), and have also compared them with other technologies such as shear wave ultrasound elastography (SWUE) (12). However, it has yet to be determined whether there is a relationship between their variables.

In addition, the apparent differences in respect to intrinsic factors of the individuals should be taking into account. The main differences might be related to muscle mass or fat, skin and fascia thickness, which may vary between the population (13–16). Moreover, asymmetries in other neuromuscular proprieties have already been documented in young athletes between dominant and non-dominant limbs (17,18). Given the fact that MMT might be more influenced by the viscoelastic proprieties of these tissues than TMG (19,20), it would be interesting to know whether these differences in the morphology characteristics may influence the relationship between both devices when comparing the dominant and non-dominant limb and gender.

The aim of this study is to analyze the data obtained from the measurements obtained from both devices, and to observe if there is any correlation between the *Dm* and *Stiffness* variables of TMG and MMT. Additionally, possible differences between the dominant and the non-dominant sides and gender will also be assessed. Taking into account the above, our hypothesis is that there should be a strong negative correlation between both variables *Dm* and *Stiffness*. However, we believe that this degree of correlation could vary. Specifically, we believe that it could be stronger in the dominant leg than in the non-dominant leg.

METHODS

Study participants

A sample calculation was performed with the GRANMO 7.12 program. It was based on the reference population of Spanish students in the 2018-2019 academic course (n=1595039), estimating a proportion of 0.11% of students in the province of Barcelona, according to the data of the Institut d'Estadística de Catalunya (Idescat). With a confidence level of 5%, 151 subjects were needed. Due to organizational reasons in the recruitment, it was carried out in groups of 10 people. Finally, 154 subjects were recruited, more than those necessary.

An observational study was carried out using a sample of a hundred and fifty-four young adult volunteers from the Faculty of Medicine and Health Sciences. Sample characteristics show that 62 of the 154 volunteers were women (40.3%) and 92 were men (59.7%). The average age of the sample was 23.8 years (SD±5.62), with an average height of 176.4 cm (SD±24.39), and an average weight of 69.04 kg (SD±13.82). The Body Mass Index (BMI) average was 22.37 Kg/m^2 (SD±3.18).

The study protocol was approved by the local ethics committee (CER-UIC-Barcelona; study code: CBAS-2018-29), respecting data protecting laws according to the Helsinki declaration. All participants signed an informed consent before enrolling the study.

The inclusion criteria were the following: (a) age between 18 and 40 years; (b) healthy subjects with no lower limb pathology.

Exclusion criteria included: (a) pregnant women; (b) subjects presenting neurologic problems during the last year; (c) having received any lower limb surgical interventions during the last six months; and (d) musculoskeletal alterations that did not allow the subject to perform the study protocol.

Subjects were informed to come in the following conditions: (a) no strenuous exercise over the previous 48h; (b) no intake of energy drinks or supplements over the previous 48h; (c) no caffeine or alcohol over the previous 3h; (d) no food intake 2h before coming to the study.

Measurements

Demographic and anthropometric variables were collected at the beginning of the study. The NMF analysis was performed in the gastrocnemius medial and lateral muscles in both dominant and non-dominant legs. These muscles are easy-to-measure and widely studied (12,21,22). Subjects were placed lying prone over a stretcher and with a foam cushion under their ankles to get a small knee flexion and neutral ankle position in order to release gastrocnemius tension (22). Same position was performed for both TMG and MMT measurements. The measuring locations were selected by manually palpating the lateral and medial gastrocnemius to locate the thickest part of each muscle. If needed, subjects were asked to perform an isometric contraction of the gastrocnemius muscle, in order to obtain the maximum displacement point of the muscle belly. Once located, a mark was made in order to ensure the measurement uniformity (23). The same locations were chosen for TMG and MMT measurements.

The TMG evaluation was done by using a Dc–Dc Trans-Tek® transductor (GK 40, Panoptik d.o.o., Ljubliana, Slovenia) that was perpendicularly placed to the tissue. Two self-adhesive electrodes (TMG electrodes, TMG-BMC d.o.o., Ljubljana, Slovenia) were placed equidistant, proximal (anode) and distal (cathode) to the sensor, with an inter-electrode distance of 5 cm *(Figure 1A)*. Patient was placed in prone position with a foam Electrical stimulation was applied through a TMG-100 System electrostimulator (TMG-BMCd.o.o., Ljubljana, Slovenia). The amplitude was progressively increased from 20 to 100 mA by 20 mA increments until there was no further increase in Dm or maximal stimulator output was reached (i.e 110mA) (24). Ten seconds rest was given between the stimuli to minimize the effects of fatigue and potentiation (25).

MMT was measured with a MyotonPro (MytonPro, Myoton Ltds., Estonia). The device was placed on the surface of the skin, perpendicular to the tissue, and located over the maximum displacement point of the muscle belly. From this position, small pressure was made against the tissue by the MyotonPro so that the device could make three short applications of pressure (15 ms) on the skin *(Figure 1B)*.

Statistical analysis

For the statistical analysis, the software SPSS 21.0 was used. The variables assessed were maximal *radial displacement (Dm)* measured with TMG, and *Stiffness* measured with MMT. Descriptive analysis was carried out. Moreover, distinction between dominant and non-dominant side was made. For quantitative variables, mean and standard derivations were calculated. Suitability of using parametric or non-parametric tests was verified by using Kolmogorov-Smirnov test. Comparison between dominant and non-dominant sides was performed by using a paired sample t-test or Wilcoxon test, and comparison between gender with unpaired t-test or Mann-Whitney U test, according to the type of variable used. Correlation analysis was performed by using Pearson's correlation coefficient or Spearman's rank correlation coefficient, depending on the type of variable assessed.

The following intervals were used in order to interpret the strength of the correlation coefficient between Dm and Stiffness: 0-0.10 negligible correlation, 0.10-0.39 weak correlation, 0.40-0.69 moderate correlation, 0.70-0.89 strong correlation, and 0.90-1.00 very strong correlation (26).

RESULTS

The descriptive outcomes of the total 154 lower limbs are shown in *Table 1*. Two values of the TMG were discarded due to error in the transcription of the data.

The amplitude of the stimulus necessary to cause the maximum radial displacement was obtained in a mean of 96.33mA (SD±7.84) for the dominant medial gastrocnemius, 97.31mA (SD±7.35) for the non-dominant medial gastrocnemius, 94.44mA (SD±9.03) for the dominant lateral gastrocnemius and 98.98mA (SD ±4.96) for non-dominant lateral gastrocnemius.

The descriptive analysis of the sample that compared dominant with non-dominant limbs *(Table 1),* shows a statistically significant difference for the *Dm* variable of the lateral gastrocnemius (p=0.039). The rest of the values of the sample show no statistically significant differences according to dominance. *Table 2* shows a subgroup analysis regarding gender. Only the *Dm* variable of the lateral gastrocnemius men shows a statistically significant difference (p<0.001). Moreover, comparison between men and women show significant differences (p<0.001) in the Stiffness of the medial and lateral gastrocnemius, both dominant and non-dominant.

The correlation analysis differentiating dominant from non-dominant limbs *(Table 3)* shows significant negative correlation for lateral gastrocnemius r=-0.278 (p<0.001) in the dominant lower limbs, and rho=-0.248 (p=0.002) in the non-dominant lower limbs. Medial gastrocnemius *Dm – Stiffness* correlations for the dominant and non-dominant lower limbs were r=-0.207 (p=0.010) and rho=-0.163 (p=0.043) respectively.

When the correlation between both *Dm* and *Stiffness* variables is analyzed according to gender *(Table 4),* statistical significance is found in the dominant lateral gastrocnemius muscle of women (r=-0.310, p=0.014). Regarding men, statistical significance is found in the dominant lateral gastrocnemius muscle (r =-0.364, p<0.001) and in the non-dominant (r=-0.214, p=0.041), as well as in the dominant medial gastrocnemius (rho=-0.225, p=0.032) and in the non-dominant (rho=-0.297, p=0.004).

DISCUSSION

The present study was carried out with the aim to analyze if there is any correlation between *maximal radial displacement* (measured with TMG) and *Stiffness* (measured with MMT) in the medial and lateral gastrocnemius muscles. To our knowledge, this is the first study investigating the relationship between these new technologies.

As both technologies seem to evaluate tissue stiffness, it was hypothesized that there should be a strong correlation between *maximal radial displacement (Dm)* and *Stiffness* variables.

First, it is important to note that our results of *Dm* are similar to those obtained in other studies that analyzed healthy adults. For example, Macgregor et al. (23) and Baraja-Vegas et al. (27) obtained a *Dm* for the GM of 3.3 mm (SD±1.2) and 3.65 mm (SD±1.03) respectively. Simola et al. (28) found a Dm for the GL of 5.7 mm (SD±2.7). Regarding *Stiffness*, our results are slightly lower compared with other studies. Li et al. (29) obtained values for the GL of 340.82 N/m (SD±69.25) and for the GM of 297.52 N/m (SD±44.45). For their part, Feng et al. (12) obtained values of 329.50 N/m (SD±54.85) and 306.80 N/m (SD±32.16) respectively.

The results show that correlation between *Dm* and *Stiffness* is negative for lateral (r=-0.278 and rho=-0. 248) and medial gastrocnemius (r=-0.207 and rho=-0.163) in both dominant and non-dominant limbs respectively. This means that when one increases the other decreases. These results are consistent with the idea that low Dm values are related to greater muscular stiffness (7,8) and result in greater *Stiffness* (MMT) values (10).

Although correlation is significant for both lateral and medial gastrocnemius, dominant and non-dominant, correlation coefficients are surprisingly low (r<0.400), so the predictive values are weak (26). These findings mean that there might be other factors that could influence in the assessment of the tissue stiffness with both technologies.

It is important to note that TMG focuses on muscle contractile response, whereas MMT assesses the viscoelastic so the predictive values are weak (26). In that sense, some authors claim that intrinsic factors such as subcutaneous fat thickness, skin thickness or fascia thickness may also influence the results (13–16). There is some controversy in the literature regarding those claims.

In a preliminary study with forty stroke patients, Fröhlich-Zwahlen et al. found a high negative correlation between stiffness (measured with MMT) and subcutaneous tissue for the vastus lateralis (r=-0.84), but not for medial gastrocnemius (r=0.0) (30). According to these results, Agyapong-Badu et al. claimed that fat thickness could be associated with muscle parameters in certain cases, but the relationship may not be direct. Other factors, such as age or gender could influence in fat thickness and be the cause of this correlation (31).

In fact, our results about gender differences agree with these claims. Our findings reflect, although not significantly, a stronger correlation between Dm and Stiffness in men than in women. On the one hand, this differences could be due to the tendency of men to have higher skin thickness (32). Moreover, some studies have evidenced gender differences related to fat distribution. In this sense, women tend to have a greater distribution of fat at the subcutaneous level, compared to greater visceral fat in men (33–35).

Nevertheless, other tensomyographic studies disagree on the influence of subcutaneous fat thickness on the measurement of neuromuscular proprieties (36). In fact, a study conducted by de Paula Simola et al. on fourteen young men found no significant correlation between skin-fold thickness and any TMG variables of the rectus femoris. They claimed that subcutaneous fat thickness had no implication on muscular stiffness (37).

However, a recent study carried out by Calvo-Lobo et al. evaluate the correlation between TMG proprieties and different tissues. Regarding the *Dm* parameter, they found a correlation of r=-0.32 (p=0.02) with skin thickness, r=-0.668 (p<0.001) with subcutaneous thickness, and r=-0.252 (p=0.077) with fascia thickness (36). None of them could be considered a strong correlation. Moreover, no studies that correlated MMT proprieties and fascial tissue were found. However, Bravo-Sánchez et al. founded asymmetries between the dominant and non-dominant limb in the morphologic structure of the patellar and Achilles tendons apparently caused by the prolonged practice of badminton. Surprisingly, they did not find differences between dominant and non- dominant myotonometric parameters in gastrocnemius muscles (38).

When comparing the correlation between *Dm* and *Stiffness,* dividing dominant from non-dominant limbs, the correlation was higher on the dominant side in both lateral and medial gastrocnemius *(Table 4)*. Although it was not measured, our first suspect was that in the dominant side fascia thickness would be higher, therefore MMT assessment would be more similar to TMG, as there were no other tissues interfering in the measures. In fact, an study conducted by Alvarez et al. in male soccer players founded no differences between dominant and non-dominant *Dm* in gastrocnemius muscles (39). However, Li et al. also founded no difference between dominant and non-dominant *Stiffness* measured with myotonometry in gastrocnemius muscles (29).

Based on these results, it can be affirmed that both tools are rather independent, and their values cannot be extrapolated when assessing muscular stiffness in clinical practice.

Therefore, one must be careful when comparing different studies addressing neuromuscular proprieties measured, especially using these two technologies.

There are some limitations in this study. Firstly, as previously mentioned, no subcutaneous fat and fascial thickness were measured. Furthermore, TMG protocol measurement set a time rest of 10 seconds between measurements when the intensity of the electrostimulation was increasing, in order to obtain the maximal radial displacement (8,9,15,23,40). However, there is little evidence that supports the use of this protocol. A recent study by Wilson et al. 2018 recommends an increased rest time of 30 seconds between measurements to avoid possible modifications due to fatigue or post-activation potentiation (14). It is possible that this phenomenon could have altered the results obtained in both TMG and MMT. Moreover, the same author recommended an inter-electrode distance of 7 cm as the optimal distance to assess gastrocnemius muscles (22).

Further studies analyzing other possible factors that may influence these variables are needed in order to have a global comprehension of the relationship between TMG and MMT.

CONCLUSION

The weak correlation between *Dm* and *Stiffness* may indicate that they assess different aspects of neuromuscular function (NMF). TMG and MMT are independent tools, and their values cannot be extrapolated when assessing muscular stiffness. There might be some other factors that influence this relationship; therefore, more studies are needed in order to better understand the correlation.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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Table 1: Outcome dividing dominant from non-dominant leg for all sample

		Dominant	Non-Dominant	
	N	Mean ± SD	Mean ± SD	p-value
Tensiomyography				
Dm - Lateral Gastrocnemius	153	5.77 ± 2.19	5.24 ± 2.30	0.039*
Dm - Medial-Gastrocnemius	153	3.55 ± 1.61	3.38 ± 1.57	0.271**
Myotonometry				
S – Lateral Gastrocnemius (N/m)	154	262.69 ± 35.93	262.06 ± 32.81	0.874*
S – Medial Gastrocnemius (N/m)	154	250.39 ± 27.11	248.80 ± 25.58	0.596*

N, Number; SD, Standard deviation; Dm, Maximal radial displacement; S, Stiffness;

* Paired t-test; ** Wilcoxon test,

Table 2: Outcome dividing dominant from non-dominant leg for gender

	Women				Men			
		Dominant	Non-Dominant			Dominant	Non-Dominant	
	N	Mean ± SD	Mean ± SD	p-value	N	Mean ± SD	Mean ± SD	p-value
Tensiomyography								
Dm - Lateral Gastrocnemius	62	5.69 ± 2.01	5.39 ± 2.27	0.263*	91	5.83 ± 2.31	5.14 ± 2.33	0.001*
Dm - Medial-Gastrocnemius	62	3.65 ± 1.63	3.37 ± 1.41	0.130**	91	3.49 ± 1.60	3.38 ± 1.69	0.449**
Myotonometry								
S – Lateral Gastrocnemius (N/m)	62	238.13 ± 23.40	240.13 ± 24.37	0.276*	92	279.24 ± 33.41	276.85 ± 29.38	0.373*
S – Medial Gastrocnemius (N/m)	62	235.76 ± 21.32	234.40 ± 20.50	0.524*	92	260.25 ± 26.04	258.45 ± 24.19	0.382*

N, Number; SD, Standard deviation; Dm, Maximal radial displacement; S, Stiffness; * Paired t-test; ** Wilcoxon test,

Table 3: Correlations dividing dominant from non-dominant leg for all sample

	Dominant	Non-Dominant
Dm vs Stiffness Lateral Gastrocnemius	-0.278 (p<0.001)*	-0.248 (p=0.002)**
Dm vs Stiffness Medial Gastrocnemius	-0.207 (p=0.010)*	-0.163 (p=0.043)**

Dm, Maximal radial displacement; *r, Pearson Correlation test; **rho, Spearman Correlation test.

Table 4: Correlations dividing dominant from non-dominant leg for gender

		Dominant	Non-Dominant
Women	Dm vs Stiffness Lateral Gastrocnemius	-0.310 (p=0.014)*	0.033 (p=0.799)*
	Dm vs Stiffness Medial Gastrocnemius	-0.184 (p=0.152) *	-0.003 (p=0.990)**
Men	Dm vs Stiffness Lateral Gastrocnemius	-0.310 (p=0.014)*	-0.214 (p=0.041)*
	Dm vs Stiffness Medial Gastrocnemius	-0.225 (p=0.032)**	-0.297 (p=0.004)**

Dm, Maximal radial displacement; *r, Pearson Correlation test; **rho, Spearman Correlation test.

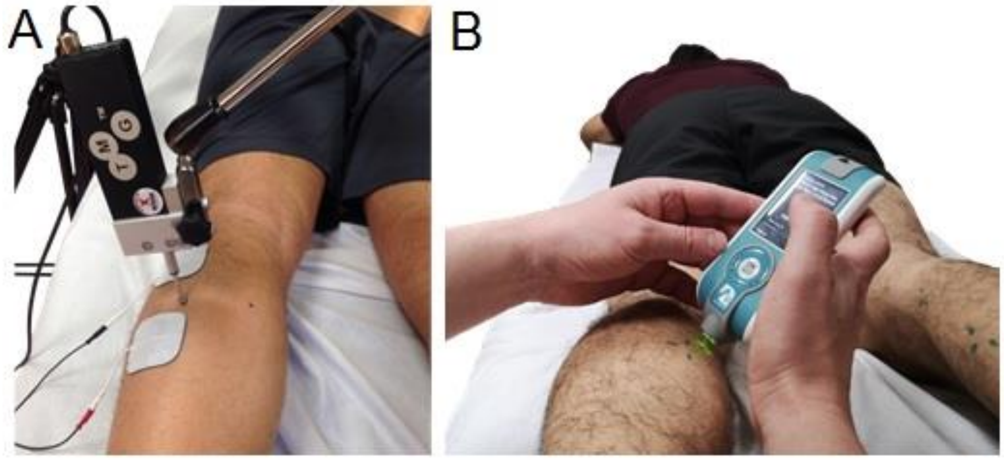

Figure 3: A.- Tensiomyography; B.- Myotonometry

Artículo 2

Artículo 2	
Publicación	Correlation between physical performance and tensiomyographic and myotonometric parameters in older adults
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Correlation between physical performance and tensiomyographic and myotonometric parameters in older adults.

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ABSTRACT

Purpose: To examine the correlation between physical performance and muscle strength and the variables obtained from tensiomyography and myotonometry.

Design: Observational study.

Methods: Fifty-two older adults able to complete functional tests participated in the study. Maximal radial muscle displacement and contraction time using tensiomyography, and muscle stiffness using myotonometry on rectus femoris and vastus lateralis were assessed. Physical performance (Short Physical Performance Battery, Timed Up and Go, Five Times Sit to Stand, and walking speed), isometric knee extension strength and grip strength were assessed. A correlation analysis was performed between all the variables.

Results: A significant correlation between the Short Physical Performance Battery and the rectus femoris (rho=0.491) and vastus lateralis Dm (rho=0.329) was found. Significant correlations between the Five Times Sit to Stand test and the Dm values of the rectus femoris (rho=-0.340) and Dm (rho=-0.304), and stiffness (rho=-0.345) in the vastus lateralis were also found. No significant correlations were found between tensiomyography and myotonometry, and the Timed Up and Go and walking speed, nor between tensiomyography and myotonometry and grip strength and isometric knee extension strength.

Conclusions: Functional tests should be prioritized in the assessment of older adults, but further research into muscle quality using technology is advisable.

KEYWORDS

elderly, physical functional performance, tensiomyography, myotonometry, muscle quality

Introduction

Recently, the World Health Organization (WHO) has defined Healthy Aging as "the process of developing and maintaining functional capacity that enables well-being in old age"(1). In this way, the focus has been placed on the relevance of preserving, as far as possible, the functional status of the older adult, in order to prevent, delay or mitigate the consequences of age-related pathologies.

Moreover, the *European Working Group on Sarcopenia in Older People (EWGSOP)* in a recent consensus has included the importance of assessing strength and physical performance as main factors when diagnosing a pathology as prevalent in older adults as sarcopenia(2). For this purpose, different functional tests such as the grip strength measurement, the sit-to-stand test, or the Short Physical Performance Battery (SPPB) have usually been used(3,4). In addition, the EWGSOP comments on the importance of assessing not only muscle quantity, but also muscle quality (micro and macroscopic aspects of muscle architecture and composition); recognizing the difficulty in establishing a precise definition, as well as the lack of devices that are currently capable of assessing it(2).

New technologies, together with current knowledge of physiology, have made it possible to assess muscle quality. Among these technologies, tensiomyography and myotonometry stand out(5). Tensiomyography is a valid and reliable assessment method(6) used to evaluate muscle quality by measuring the radial displacement of the transverse fibers of the muscle belly as a function of contraction time. Previous studies have shown that tensiomyography is capable of assess the proportion of type I fibers in a muscle. Lower Tc values would be related to a lower proportion of slow fibers(7). In older adult populations, there is an increase in muscle contraction time, caused by a decrease in type II fibers(8), which are activated mainly in actions requiring strength and speed(9). On the other hand, tensiomyography has also been able to detect changes in muscle stiffness in a phase of atrophy during a period of immobilization (10). A single study has studied the relationship between physical performance and tensiomyography in older adults, founding contradictory results(11). Myotonometry is another reliable non-invasive assessment method used to evaluate the viscoelastic properties of tissues(12) different parameters from those observed in tensiomyograpghy(13). There are currently no studies linking myotonometry and physical performance. The lack of studies with both technologies in older adults makes it difficult to establish the normative values for this population.

Knowing the changes that occur in muscle quality through the use of new technologies, and how these changes are related to physical performance, will make it possible to optimize the screening process of older adults. This could allow us to identify those at risk for negative events (risk of falls, frailty etc.) and be able to establish prevention strategies, as well as a objectively monitor their evolution. To date, it is still unclear whether there is a direct relationship between the deterioration in muscle quality and the decrease in strength and physical performance in the elderly. The main objective of the present project is to analyze the level of correlation between the physical performance and muscle strength tests, and the variables obtained from tensiomyography and myotonometry.

Materials and Methods

Participants

Participants were non-randomly recruited according to their availability to participate through the Research Ethics Committee of the Universitat Internacional de Catalunya (CBAS-2020-12). Inclusion criteria were: a) people over 65 years of age. Exclusion criteria were: a) inability to stand or ambulate unassisted, b) previous bone fracture during the last 6 months, c) uncontrolled and symptomatic cardiovascular or respiratory disease, d) current cancer, e) inability to understand the information provided by the evaluators.

The G*Power software (version 3.1) was used to calculate the sample size. For the main variable SPPB no previous studies were found, so a moderate correlation level of r=0.45 was predicted. For the second main physical performance variable Timed up and go (TUG), the sample size was calculated using the data obtained in a similar study by Fabiani et al(11). In the study, authors found a correlation between contraction time (Tc) and TUG of rho=0.456 in the vastus lateralis quadriceps musculature. Establishing an α error of 0.05, and a statistical power of 0.95, and assuming losses of 10% due to possible errors in data transcription, a sample size of 50 subjects was obtained for the SPPB and 52 for the TUG. Choosing the higher value, the sample size was set at 52 subjects.

Procedure

Once the subjects were contacted, they were confirmed to meet the inclusion/exclusion criteria before the evaluation. First, personal data were recorded, as well as height and weight and dominance. Next, tensiomyography and myotonometry tests were performed on the rectus femoris and vastus lateralis muscles of the dominant limb. Isometric knee extension strength was assessed with a hand-held dynamometer. Finally, functional tests (SPPB, TUG, 5XSST and 4-meter walking speed) and grip strength assessment were performed.

Variables

Main variables:

Maximal radial muscle displacement (Dm): Measured by tensiomyography(6,14). Indicates the maximum radial displacement measured in millimeters of the muscle when subjected to involuntary contraction by electrostimulation(13). The rectus femoris and vastus lateralis muscles were measured. To perform the measurement, the patient must be in a muscle relaxation position, usually in the decubitus position. Same protocol as previous studies was conducted(15).

Contraction time (Tc): Measured by tensiomyography. Indicates the time (in milliseconds) it takes for the muscle to reach from 10 to 90% of the maximum radial displacement (Dm)(15). The rectus femoris and vastus lateralis muscles were measured.

Stiffness: Measured by myotonometry. It is determined by the ratio between the force produced by the mechanical impulse and the depth of tissue deformation. Its unit of measurement is newtons per meter (N m-1). The femoris and vastus lateralis muscles were measured. To perform the measurement, the patient must be in a muscle relaxation position. Same protocol as previous studies was conducted(15).

Short Physical Performance Battery (SPPB): This is a functional test battery widely used in primary care and research. It consists of 3 tests: balance test in feet together position, semitandem and tandem for 10 seconds with eyes open; 4 meters walking test and five chair raises test. Each result in the three tests has a numerical value from 0-4 which is summed to obtain a maximum overall score of 12 points. Test-retest reliability has been shown to be good to excellent (ICC between 0.83-0.92), as well as excellent inter-rater reliability (ICC 0.91) among elderly patients(4).

Timed Up and Go Test (TUG): It reflects the time in seconds it takes the person to get up from the chair, with the help of the arms, walk 3 meters as fast as possible, turn around an obstacle, return to the chair and sit down again. The test was performed twice and the one with the shorter time was chosen. Its reliability has been previously studied (ICC=0.98, 95%CI=0.93-1.00; SEM=0.7).

Secondary Variables:

Five-Times Sit to Stand Test (5XSST): It reflects the time in seconds it takes the person to sit down and stand up five times from a chair with a backrest, without the help of the arms. It is included in the SPPB battery, but its score has individual value by itself. The test was performed twice and the one with the shorter time was chosen(2).

4 Meters Walking Test (4WT): It reflects the time in seconds it takes a person to complete 4 meters at normal speed. It is included in the SPPB battery, but its score has individual value by itself. The test was performed twice and the one with the shortest time was chosen. Its reliability has been previously studied (ICC=0.96, 95%CI=0.94-0.98; SEM=0.01)(16).

Handgrip strength: Measured by hand dynamometry. Its unit of measurement is kilograms (Kg). (17). The Jamar® dynamometer device was used. To perform the measurements, the subject was placed in a seated position on a chair, resting on the backrest, with the feet on the floor and with the arms resting, ensuring 90º elbow flexion and the wrist in neutral position. Both dominant and non-dominant arms were measured. Three measurements were taken for each hand alternately, with a one-minute rest between measurements. The mean of the three measurements for each hand was calculated and the hand with the best results was chosen. The validity and reliability of this device has been evaluated in previous studies (ICC=0.98)(18).

Muscular strength: Measured with hand-held dynamometry. Its unit of measurement is kilograms (Kg). Knee extension of the dominant limb is measured. It is a valid and reliable method (ICC=0.78, 95%CI=0.63-0.92; SEM=13.87) (19). The hand-held dynamometer MicroFET 2® device was used. (20). During the measurement, a strap was placed to fix the dynamometer to the subject, in such a way as to ensure that the contraction was isometric. Three measurements were taken for each movement, and the average of the three was calculated.

Statistical analysis

Statistical analysis was performed with the Jamovi v.1.6.23 software. Descriptive statistics were calculated for all variables. Quantitative variables were expressed as mean and standard deviation and qualitative variables were expressed as number and percentage. The Shapiro-Wilk test was used to test the normal distribution of the variables. Correlation analysis was performed by calculating Pearson's correlation coefficient or Spearman's rank correlation coefficient, depending on the distribution of the variable evaluated. The significance level was set at 0.05 with a 95% confidence interval. The following intervals were used to interpret the strength of the correlation coefficient: 0-0.10 insignificant correlation, 0.10-0.39 weak correlation, 0.40-0.69 moderate correlation, 0.70-0.89 strong correlation and 0.90-1.00 very strong correlation(21).

Results

Characteristics of the 52 participants are shown in Table 1. Descriptive values of the variables are presented in Table 2. Of the data of 52 participants, 2 values of the tenisomyography variables were lost due to an error in the transcription of the data. Similarly, 2 values of handgrip, 1 of SPPB and 1 of TUG were lost. None of these losses exceeded 10% of the losses assumed in the sample calculation.

Table 1. Anthropometric data of the sample

Variable	Mean (SD) or N (%)
Sex	
Male	31 (60%)
Female	21 (40%)
Dominance	
Right	50 (96%)
Left	2 (4%)
Age	73.7 (7.44)
Height	159 (10.3)
Weight	67.4 (80.5; 60.1)*
BMI	28.3 (4.12)

*, median (Q1; Q3); BMI, body mass index; Median (IQR); SD, standard deviation.

Table 2. Descriptive analysis of the variables

Variable	Mean (SD)
SPPB	12 (12; 11)*
TUG	8.50 (10.1; 7.39)*
5XSST	10.3 (11.9; 9.43)*
WS	1.07 (0.26)
HHD-KE	37.8 (15.8)
HG	30.4 (39.9; 21.1)*
Dm-RF	4.28 (2.26)
Tc-RA	44.6 (14.7)
St-RA	292 (45.1)
Dm-VL	2.34 (3.42; 1.13)*
Tc-VL	34.2 (58.2; 23.4)*
St-VL	311 (36.7)

*, median (Q1; Q3); 5XSST, five-times sit to stand test; Dm, maximal radial muscle displacement; HG, hangrip strength; HHD-KE; hand-held dynamometry knee extension; RF, rectus femoris; SD, standard deviation; St, stiffness; SPPB, short physical performance battery; Tc, contraction time; TUG, timed up and go test; VL, vastus lateralis; WS, walking speed.

Table 3 shows the correlation matrix between the different physical performance assessment tests and the tensiomyography and myotonometry variables. The correlation analysis shows a significance between the SPPB test and the values of Dm of the rectus femoris (rho=0.491, p<.001) and Dm of the vastus lateralis (rho=0.329, p=.021) and the 5XSST test and the values of Dm of the rectus femoris (rho=-0.34, p=. 016), vastus lateralis Dm (rho=-0.304, p=.032) and vastus lateralis stiffness (rho=-0.345, p=.012).

Table 3. Correlation matrix

		Dm-RF	Tc-RA	St-RA	Dm-VL	Tc-VL	St-VL
SPPB	Correlation	**0.491**†	0.137†	0.073†	**0.329**†	0.113†	0.273†
	p-value	< .001	0.348	0.609	0.021	0.438	0.053
TUG	Correlation	-0.172†	0.103†	0.101†	-0.067†	0.032†	0.040†
	p-value	0.237	0.483	0.481	0.645	0.825	0.780
5XSST	Correlation	**-0.340**†	-0.038†	-0.108†	**-0.304**†	-0.076†	**-0.345**†
	p-value	0.016	0.793	0.447	0.032	0.602	0.012
WS	Correlation	0.093*	-0.076*	-0.174*	0.094†	0.036†	-0.098*
	p-value	0.522	0.601	0.216	0.518	0.804	0.490
HG	Correlation	0.140†	0.129†	0.002†	-0.047†	-0.017†	-0.092†
	p-value	0.341	0.383	0.992	0.752	0.907	0.535

HHD-KE	Correlation	0.220*	-0.088*	0.092*	0.115†	-0.085†	0.108*
	p-value	0.125	0.542	0.515	0.428	0.557	0.448

*, Pearson's correlation coefficient; †, Spearman's rank correlation coefficient; 5XSST, five-times sit to stand test; Dm, maximal radial muscle displacement; HG, hangrip strength; HHD-KE; hand-held dynamometry knee extension; RF, rectus femoris; St, stiffness; SPPB, short physical performance battery; Tc, contraction time; TUG, timed up and go test; VL, vastus lateralis; WS, walking speed.

Discussion

The aim of this study was to analyze the level of correlation between the functional and muscle strength tests, and the variables obtained from tensiomyography and myotonometry. With respect to the descriptive values, all the variables obtained in the functional tests, as well as the grip strength, were found to be above the cut-off points defined by the EWGSOP for the diagnosis of sarcopenia(2). This is a population that would be at low risk of suffering future negative events, such as care dependency, falls, fractures or mortality(4). Regarding tensiomyography and myotonometry values, there are no normative values for the knee extensor musculature in the older adult's population. Thus, the results of the present study allow us to know the values for a healthy population. Fabiani et al 2021(11) analyzed, in a sample of 28 women over 65 years of age, the Tc for the vastus lateralis quadriceps muscle, obtaining a slightly higher contraction time. Similarly, regarding the Dm of the vastus lateralis, his results were superior. No studies were found that assessed the rectus femoris in this population. Regarding myotonometry, Agyapong-Badu et al. published an article in which they analyzed the Stiffness of the rectus femoris in a similar population(22). In all three studies, the values were higher than those obtained in our sample. Comparing the results with those of a population of young people, rectus femoris stiffness was found to be lower in both a sample of inactive young people(22) and athletes(23). The stiffness results of the present study were lower than those of a population of master athletes(23). These results suggest that muscle tissue becomes stiffer with aging. A certain level of muscle stiffness could be beneficial in transmitting muscle contraction to the joints more efficiently. It would be understandable in this case that master athletes would have a higher stiffness than non-athletes. However, studies performed on the tibialis anterior and gastrocnemius anterior musculature show a decrease in stiffness with age(24).

Regarding the correlation analysis, a statistically significant moderate positive correlation was found between the SPPB battery and the Dm of the rectus femoris and vastus lateralis quadriceps musculature. In addition, a statistically significant weak negative correlation was found between the 5XSST test and the Dm of the rectus femoris and vastus lateralis quadriceps musculature. These results would indicate that a better physical performance would be related to higher Dm values. Previous studies on the topic are contradictory. On the one hand, studies conducted by Pišot et al.(25) and Šimunič et al.(10) in which a 35-day period of bed rest resulted in an increase in Dm. These results would indicate an increase in Dm in a period of disuse muscle atrophy. It should be noted that the participants in both studies were young adults. On the other hand, Paravlić et al.(26) found a decrease in Dm in the knee extensor musculature after one month of undergoing total knee arthroplasty in older adults. The only study correlating physical performance and Dm for an older adult population is the study by Fabiani et al.(11). In agreement with the results of the present study, they found a negative correlation between both variables. The possible hypothesis proposed by the authors regarding these results was that the infiltration of fat and connective tissue within the muscles produced in aging could influence this correlation. In our opinion, it seems that this hypothesis has not yet been demonstrated; however, in view of the results, it would seem clear to differentiate muscle atrophy produced by disuse from muscle atrophy related to aging.

Regarding myotonometry, a statistically significant weak negative correlation was also found between the 5XSST test and vastus lateralis quadriceps stiffness. This correlation would imply that people with low physical performance would have greater stiffness. No previous studies have been found to corroborate the present results. Only the study by Agyapong-Badu et al. (27) generated a musculoskeletal health status discrimination model based on different functional tests and technologies, including the Myoton. No statistical significance was found for the rest of the functional tests, nor for the strength tests.

To our knowledge, until now only the article by Fabiani et al.(11) correlated tensiomyography with physical performance assessment tests (specifically with the TUG test). In addition to the previously discussed Dm values, they found a moderate negative correlation between TUG values and vastus lateralis Tc values. These results would imply that a decrease in contraction time would be related to a lower level of physical performance. It is plausible to conclude from the study of Fabiani et al.(11) that this decrease in the number of type II fibers could be the cause of the decrease in physical performance. In this sense, Zubac et al.(28) performed a plyometric training intervention in older adults, obtaining significant improvements in the countermovement jump take-off speed (CMJ) and a decrease in Tc. Likewise, Šimunič et al.(8) conducted an observational study, in which they demonstrated that master athletes in power sports maintained lower Tc values than a group of non-athlete older adults. Unfortunately, the results of the present study show no correlation between contraction time and physical performance, so further studies will be necessary to confirm this hypothesis.

As recommended by the EWGSOP in its latest consensus, it is a priority to identify which indicators of muscle quality best predict the loss of muscle mass, strength and function. In the same way, it raises the question of how and through which tools muscle quality can be accurately and affordably assessed(2). In this sense, tensiomyography appears as a tool with potential in this field. Unfortunately, there are still few studies using this tool in older adults. The Dm variable could be used to quickly and easily identify those people who are in a situation of loss of physical performance, especially those whose condition does not allow them to perform functional tests (hospitalized people, or those with limitations in ambulation).

Regarding the limitations of the study, it should be taken into account that both tensiomyography and myotonometry are tools for assessing the muscular quality of a muscle in isolation, and without the participation of the central nervous system. Among the factors that influence physical performance, intermuscular coordination and the processing of information to conduct the task in question have a great influence on the final result of the functional test(29). In this sense, it is normal that the correlation levels are moderate. As for the population, the recruitment of the sample included a relatively low percentage of subjects considered "frail". Including a broader spectrum of the older adult population in future studies will allow a better understanding of these relationships.

To sum up, there is a correlation between the SPPB test and the rectus femoris and vastus lateralis Dm values. There is a correlation between the 5XSST and the Dm values of the rectus femoris and Dm and stiffness in the vastus lateralis. No significant correlations were found between tensiomyography and myotonometry, and the functional tests of TUG and walking speed. No significant correlations were found between tensiomyography and myotonometry and handgrip strength and isometric knee extension strength. In view of these results, the authors conclude that functional tests should be prioritized in the assessment of the older adult; however, it is advisable to continue studying the technologies that allow the assessment of muscle quality.

Declaration of interest statement:

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Artículo 3

Artículo 3	
Publicación	Correlation between Physical Performance and Stabilometric Parameters in Older Adults
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del **doctorando**	del artículo

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Correlation between Physical Performance and Stabilometric Parameters in Older Adults

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Abstract: *Background and Objectives*: Falls are a common and serious threat to the health and independence of older adults. The decrease in functional capacity during aging means an increased risk of falls. To date, it is not known whether there is a relationship between balance and functional tests. The aim of the study was to evaluate the correlation between eyes-open and eyes-closed static balance with different functional tests. *Materials and Methods*: A correlation study was designed with 52 healthy subjects over 65 years of age. *Results*: Regarding the open eyes stabilometric parameters, significant correlations observed between the surface and the functional tests were weak in all cases. The correlations observed between length and the functional tests performed were moderate, except for that of the Timed Up and Go test (TUG) which was weak. No significant correlation between TUG and surface was found. Regarding the closed eyes stabilometric parameters, statistically significant moderate correlations were found between the surface and the Short Physical Performance Battery (SPPB) and the Five Times Sit to Stand test (5XSST). In the case of the length with eyes closed, a statistically significant moderate correlation (rho = 0.40–0.69) was found with the SPPB and 5XSST variables, and weak correlations with the 4 m Walk Speed test (4WS) and TUG variables. *Conclusions*: There is a mild to moderate correlation between some functional tests and stabilometric parameters in adults over 65 years old.

Keywords: physical functional performance; elderly; postural balance; accidental falls; stabilometry

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Correlation between physical performance and stabilometric parameters in older adults.

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ABSTRACT

Background and Objectives: Falls are a common and serious threat to the health and independence of older adults. The decrease in functional capacity during aging means an increased risk of falls. To date, it is not known whether there is a relationship between balance and functional tests. The aim of the study was to evaluate the correlation between eyes-open and eyes-closed static balance with different functional tests. *Materials and Methods*: A correlation study was designed with 52 healthy subjects over 65 years of age. *Results*: Regarding the open eyes stabilometric parameters, significant correlations observed between the surface and the functional tests were weak in all cases. The correlations observed between length and the functional tests performed were moderate, except for that of the Timed Up and Go test (TUG) which was weak. No significant correlation between TUG and surface was found. Regarding the closed eyes stabilometric parameters, statistically significant moderate correlations were found between the surface and the Short Physical Performance Battery (SPPB) and the Five Times Sit to Stand test (5XSST). In the case of the length with eyes closed, a statistically significant moderate correlation (rho = 0.40–0.69) was found with the SPPB and 5XSST variables, and weak correlations with the 4 m Walk Speed test (4WS) and TUG variables. *Conclusions*: There is a mild to moderate correlation between some functional tests and stabilometric parameters in adults over 65 years old.

KEYWORDS

physical functional performance; elderly; postural balance; accidental falls; stabilometry

1. Introduction

Falls are a common and serious threat to the health and independence of older adults. According to data from the Centers for Disease Control, approximately one in three older adults suffers a fall each year [1]. In addition, one in five falls results in se-rious injuries, such as broken bones or head injuries. More than 95% of hip fractures and up to 2.8 million emergency treatments for fall injuries occur each year [2]. In addition, the mortality rates are 20–35% and, of those who survive, between 30% and 45% [3,4] do not recover the functionality of prior to the fracture [5].

Although falls are multifactorial in nature, balance impairment has been identified as one of the main intrinsic risk factors for falls [6]. Physical performance and balance generally decline with ageing, leading to an increased risk of falls for many older adults, especially those who are inactive or insufficiently active [7].

Although there is no universally accepted definition of human balance [8,9], in the clinical setting it can be defined as the inherent ability or postural control of a person to maintain, achieve, or restore a specific state of balance and not to fall [10]. Relevant parameters are the obtained surface area of the ellipse and the length of the stabilogram. However, the cost of stabilometry can be very high and for this reason the assessment of balance in older adults is complicated outside the research setting. Differences in the stabilometry parameters have appeared depending on muscle condition [11] or physical activity level [12], and an alteration in stabilometry has also been seen in different pathological processes [13–15].

Physical performance has been defined as an objective measure of body function related to locomotion [16]. In addition, it is closely related to the state of health [17–21], and a significant association between fall risk and muscle weakness has been observed [22]. Results of functional tests such as the Short Physical Performance Battery (SPPB) [19] or the walking speed test [17] have also been shown to be associated with the risk of falls [23], disability [21], and even mortality [19,20]. These functional tests are frequently useful in the clinical field and experts recommend that all older adults be screened for physical performance in primary care to detect those at risk for frailty and/or sarcopenia [16].

In this way, the literature shows that interventions focused on improving func-tional capacity have also proven to be effective in reducing falls and balance [24]. Therefore, it is reasonable to think that there is a direct relationship between physical performance and balance. However, currently, no study has been found that correlates those variables. If there is a correlation between the two, using functional tests instead of a stabilometric platform may be a more affordable option for the clinical setting.

The aim of this study was to evaluate the correlation between eyes-open (OE) and eyes-closed (CE) static balance with different functional tests in people over 65 years old.

The hypothesis of this study was that there is a statistically significant correlation between OE and CE static balance and different functional tests in people over 65 years old.

2. Materials and Methods

2.1. Study Design

A cross-sectional observational correlational study was performed.

2.2. Sample Size Calculation

The GRANMO v 7.12 program was used to calculate the sample size. A correlation coefficient analysis was performed with an alpha risk of 0.05, bilateral contrast, beta risk of 0.20, a moderate Pearson correlation coefficient estimate of 0.4 and a loss forecast of 10%, and a necessary sample of 52 subjects was obtained.

2.3. Participants

Fifty-two volunteers were recruited through the Universitat Internacional de Ca-talunya and the Associació de Gent Gran Casal Anna Murià (Tarrasa). At the university, students and faculty staff were verbally informed of the characteristics of the study and the inclusion and exclusion criteria, and our contact telephone number was left in case volunteers knew of any other person who might meet the requirements. At the senior center, a voluntary meeting was held with the users to explain the study and to obtain the contact details of persons who may be interested in participating. The participant selection process was carried out by telephone call. The measurements were carried out between October 2020 and November 2021.

Inclusion criteria were: (a) people over 65 years of age, and (b) being able to perform all the assessment tests of the study. Exclusion criteria were: (a) inability to stand or ambulate in an unassisted manner, (b) previous bone fracture in the previous 6 months, (c) uncontrolled symptomatic cardiovascular or respiratory disease, (d) current cancer under treatment, and (e) inability to understand the information provided by the as-sessors.

2.4. Outcomes

The primary variable of balance measured with stabilometry and the secondary variables of functionality were recorded through the SPPB, the 4 m walk test (4WT), the Five Times Sit to Stand test (5XSST) and the Timed Up and Go test (TUG).

Balance was assessed by means of the stabilometric variables of surface area of the elipse and length of the stabilogram. The surface of the ellipse comprises 95% of all the measured points of the center of pressures. It is measured in square millimeters. A larger surface area of the ellipse implies a lower capacity to maintain equilibrium at the center of pressure. The length of the stabilogram comprised 100% of the points recorded. It is measured in millimeters, and assesses the accuracy of the fine postural system in maintaining balance. A longer stabilogram length indicates a greater involvement of the fine control system in rebalancing. Both parameters were measured with eyes open and with eyes closed. The main difference between both measurements is that with the eyes open, the visual system is mainly involved, whereas, with the eyes closed, the vestibular system, the proprioceptive system, and the plantar receptors become more important [25,26]. Measurements were performed using the Satel 40 Hz stabilometric force plat-form (model PF2002; SATEL SARL, 6 rue du Limousin-31,700 Blagnac, France). This is a portable platform used in clinical and research settings, which has proven to be a valid and reliable tool for measuring balance in the standing position [27]. Measurements were performed in a standardized position, with the feet at a 30° angle, and the heels 2 cm apart. Subjects were positioned facing a white wall with a red plumb line 90 cm from the platform to ensure that the subject is centered. Subjects were asked to keep their arms at the side of the body and to relax as much as possible, without clenching the jaw (Figure 1). [27]. The recording time is 51.2 s

[28], determined by the platform's ability to collect 40 data per second with a conversion card (2048 data captured per minute).

Figure 1. Stabilometric measurement.

The SPPB test battery is widely used in primary care and research. It consists of 3 tests: a balance test with feet together, in semi-tandem and tandem positions for 10 s with eyes open; a walking speed test over a distance of 4 m; and a test of sitting down and getting up from a chair 5 times. Each score in the three tests has a value of 0–4, which was summed to give a maximum score of 12 points. Previous studies have es-tablished that a score equal or less than 8 points is associated with an increased risk of future negative events, such as falls, hospitalizations, sarcopenia, or frailty [19]. Test-retest reliability has been shown to be good to excellent (ICC between 0.83 and 0.92 for measurements taken one week apart), and inter-rater reliability is excellent (ICC 0.91) among acutely admitted elderly patients [23].

The 5XSST shows the time in seconds it takes a person to sit down and stand up five times from a chair with a backrest and without arm assistance. Although it is included in the SPPB battery, its score has individual value on its own. The test was performed twice and the one with the shorter time was chosen. Previous studies have established that a time greater than 15 s is associated with an increased risk of future negative events, such as frailty, sarcopenia, falls, or hospitalization [16].

The 4WS shows the time in seconds it takes a person to travel 4 m at normal speed. Although it is included in the SPPB battery, its score has individual value. The test was performed twice and the one with the shortest time was chosen. Its reliability has been previously studied (ICC = 0.96, 95%CI = 0.94–0.98; SEM = 0.01) [29]. Previous studies have established that a speed lower than 0.8 m/s (3.2 s for the 4 m) would be related to a higher risk of suffering future negative events, such as frailty, sarcopenia, falls, or hospitalization [16,30].

The TUG is a test commonly used in both consultation and research. It reflects the time in seconds it takes the person to get up from the chair, with the help of the arms, walk 3 m, turn around an obstacle, return to the chair, and sit down again. The test was performed twice and the one with the shorter time was chosen. Previous studies have established that a time above 20 s indicates the person is at risk for future negative events [16]. In addition, its reliability has been previously studied (ICC = 0.98, 95%CI = 0.93–1.00; SEM = 0.7).

2.5. Procedure

After contacting the subjects, it was verified that they met the inclusion/exclusion criteria. Before starting the study, all participants were asked to sign the informed consent form. To begin, personal data, height and weight, and dominance were rec-orded. Next, the functional tests (SPPB, TUG, 5XSST, and 4WS) were performed. Finally, stabilometry was performed in a quiet room. All measurements were performed standing, barefoot, and without socks. Measurements were repeated if the patient coughed, sneezed, yawned, turned his or her head, or performed a maximal inhalation [27]. Both OE and CE measurements were repeated twice. From the two measurements, the values having the best score were chosen [25].

2.6. Statistical Analysis

Statistical analysis was carried out with the Jamovi v.1.6.23 [Computer Software]. Descriptive statistics were calculated for all variables. Quantitative variables were ex-pressed as mean and standard deviation, and qualitative variables as number and per-centage. The Kolmogorov Smirnov test was used to test the normal distribution of the variables. Correlation analysis was performed by calculating Pearson's correlation co-efficient or Spearman's rank correlation coefficient, depending on the distribution of the variable evaluated. The significance level was set at 0.05 with a 95% confidence interval. The following intervals were used to interpret the correlation coefficient: 0–0.10 insig-nificant correlation, 0.11–0.39 weak correlation, 0.40–0.69 moderate correlation, 0.70–0.89 strong correlation, and 0.90–1.00 very strong correlation [31].

3. Results

Between October 2020 and November 2021, 52 subjects over 65 years of age (31 men and 21 women) who met all eligibility criteria and agreed to participate were recruited.

The demographic characteristics of the sample are summarized in Table 1. No adverse effects, side effects, or losses were recorded in the study.

Table 1. Anthropometric data of the sample**.**

Variable	**Mean ± SD** **n°**
Sex (Men/Female)	52 (31/21) +
Dominance Lower Limb (Right/Left)	52 (50/2) +
Dominance Upper Limb (Right/Left)	52 (50/2) +
Age (years)	73.7 ± 7.44
Height (cms)	159 ± 10.3
Weight (kgs)	67.4 (20.4) *
BMI (Kg/m^2)	28.3 ± 4.12

SD, standard deviation; +, number of cases; *, Median (Interquartile range).

After performing the Kolmogorov Smirnov test, all dependent variables in this study followed a non-normal distribution (Kolmogorov Smirnov test $p < 0.05$) with the exception of the gait speed variable (Kolmogorov Smirnov test $p > 0.05$). Table 2 records the descriptive values of the functional tests and stabilometry.

Table 2: Functional test and estabilometric parameters of the sample

	SPPB (0–12)	**5XSST (sg)**	**4WS (m/sg)**	**TUG (sg)**	**OE Surface (cm²)**	**OE Length (cm)**	**CE Surface (cm²)**	**CE Length (cm)**
Mean	11.2	12.1	1.07	9.04	215	540	306	748
Median	12.0	10.3	1.07	8.50	167	494	224	662
Standard Deviation	1.50	6.34	0.260	2.59	163	202	224	333

Interquartile Range	1.00	2.50	0.233	2.73	124	277	262	360

SPPB, Short Physical Performance Battery; 5XSST, Five Times Sit to Stand test; 4WS, 4 m Walk Speed test; TUG, Timed Up and Go test; OE, Open Eyes; CE, Closed Eyes.

The results of the correlation analysis are shown in Table 3. In the tests with OE, we observed a statistically significant correlation in all variables for both surface and length, with the exception of the surface of the TUG test.

The correlation observed for the surface with OE was, in all cases, weak. However, the correlation values that we observed for the length in the test performed with OE were moderate, except for that of the TUG test, which was weak.

Regarding the tests with CE, we observed a statistically significant moderate correlation in the SPPB and the 5XSST for the surface with CE.

In the case of the length with CE, we observed a statistically significant moderate correlation in the SPPB and 5XSST variables and a weak correlation in the 4WS and TUG variables.

Table 3. Correlation analysis.

		SPPB	5XSST	WS	TUG
OE Surface	Spearman's rho	−0.384	0.278	−0.310	0.239
	p-value	**0.005**	**0.046**	**0.025**	0.092
OE Length	Spearman's rho	−0.491	0.478	−0.448	0.324
	p-value	**<0.001**	**<0.001**	**<0.001**	**0.020**
CE Surface	Spearman's rho	−0.462	0.502	−0.265	0.256
	p-value	**<0.001**	**<0.001**	0.058	0.070
CE Length	Spearman's rho	−0.542	0.534	−0.362	0.292
	p-value	**<0.001**	**<0.001**	**0.008**	**0.037**

SPPB, Short Physical Performance Battery; 5XSST, Five Times Sit to Stand test; 4WS, 4 m Walk Speed test; TUG, Timed Up and Go test; OE, Open Eyes; CE, Closed Eyes.

4. Discussion

The aim of the present study was to evaluate the relationship between static bal-ance with OE and CE with different functional tests in people over 65 years of age.

Regarding the descriptive values, all the means of the values of the functional tests were above the cut-off points indicating risk of suffering future negative events [23]. With regard to the results of stabilometry, to date no studies have been found that assess balance with this device. The study by Rodríguez-Rubio et al. [27] assessed 42 healthy adults aged 18–65 years. Their results were lower for both surface and length in OE and CE. The results of the present study are surely different due to the age of the volunteers. This would suggest that stabilometric parameters change with increasing age (more surface and length). However, it is unclear whether these changes are due to the lower level of physical activity of older adults (as suggested in previous investigations [12]) or the age of this sample. In the neurological field, alteration of stabilometric parameters has been described in Alzheimer's disease [15], multiple sclerosis, and fragility patients [14,32].

The interpretation of the correlations observed between stabilometry and the dif-ferent variables indicates that a better score (values closer to 12) on the SPPB implies better stabilometric parameters. With regard to the 5XSST variable, we observed that the longer the time required to complete the test, the worse the values for the stabilometric parameters. In the 4WS variable, the shorter the time required to complete the test, the better the stabilometric parameters, and finally, in the TUG test, the shorter the time required to complete the test, the better the stabilometric parameters. Although there was a significant correlation in all these variables, the correlation varied between mild and moderate, so the results should be interpreted with caution.

An earlier systematic review with meta-analysis concluded that exercise interven-tions are beneficial in improving physical function by increasing muscle strength, gait speed, mobility, balance, and physical performance [26]. Indirectly, we observed this close relationship between balance and the functional capacities of the subjects. Another systematic review with meta-analysis by Gine et al. [33] examined the effects of exercise on physical function in older adults, and showed that exercise was effective in im-proving normal gait speed (MD = 0.07 m/s), fast gait speed (MD = 0.08 m/s), and SPPB score (MD = 2.18). According to different official organizations, multicomponent pro-grams focused on strength training are the best strategy to improve the physical per-formance of older adults [34,35]. In the future, it would be interesting to assess whether a multicomponent training program is able to improve both physical performance and stabilometric parameters.

Among all the functional tests, the SPPB had the highest level of correlation with the stabilometric parameters. These results are consistent, since one-third of the total score of this test is obtained in the static balance test. In this sense, it is possible that the correlations obtained are not strong because the functional tests not only evaluate bal-ance, but also strength and gait speed.

Based on the results obtained, we consider that both functional tests and stabilo-metric parameters have their clinical utility, but should not be interchanged. Functional tests would provide more general information on health status, and would be more useful in the screening process, whereas stabilometric parameters are much more spe-cific and should be used mainly in people with some type of balance or postural control impairment.

Study Limitations

The main limitation of this study is that it was only performed in healthy older adults, and we do not know if these results would follow a similar correlation in older adults having different pathologies. Another limitation we observed is that these func-tional tests can only be used in people with certain functionality, and are totally de-pendent on the patient's ability to ambulate. Finally, the fact that the level of physical activity performed by these individuals was not recorded may be a limitation to be taken into account in future projects, as there is an association between the physical activity level and the stabilometric parameters

5. Conclusions

There is a mild to moderate correlation between different functional tests and sta-bilometry in adults over 65 years old.

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Artículo 4

Artículo 4	
Publicación	Effectiveness of protein supplementation combined with resistance training on muscle strength and physical performance in elderly: A systematic review and meta-analysis
Autores	Noé Labata-Lezaun, Luis Llurda-Almuzara, Carlos López-de-Célis, Jacobo Rodríguez-Sanz, Vanessa González-Rueda, César Hidalgo-García, Borja Muniz-Pardos, Albert Pérez-Bellmunt
Revista	Nutrients
Quartil (2020)	Q1
Cita	Labata-Lezaun N, Llurda-Almuzara L, López-de-Celis C, Rodríguez-Sanz J, González-Rueda V, Hidalgo-García C, et al. Effectiveness of Protein Supplementation Combined with Resistance Training on Muscle Strength and Physical Performance in Elderly: A Systematic Review and Meta-Analysis. Nutrients. 2020 Aug 27;12(9):2607. doi: 10.3390/nu12092607. PMID: 32867103; PMCID: PMC7710730
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Participación	Primer autor
Contribución del doctorando	Diseño del estudio, Realización de la revisión sistemática, Realización del meta-análisis, Redacción del artículo

nutrients

MDPI

Review

Effectiveness of Protein Supplementation Combined with Resistance Training on Muscle Strength and Physical Performance in Elderly: A Systematic Review and Meta-Analysis

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Abstract: The aim of this study was to evaluate the effectiveness of the combination of resistance training (RT) and protein supplementation (PS), compared to RT alone or combined with a placebo (plS), in the improvement of muscle strength and physical performance. The search strategy in PubMed, Cochrane Library, and Web of Sciences databases found a total of 294 studies. Once inclusion and exclusion criteria were applied, 16 studies were included for the qualitative analysis. A total of 657 healthy elderly (>60 years) participants were analysed. Finally, 15 articles were included in the quantitative analysis with one being excluded due to issues with data availability. Upper-limb, lower-limb, and handgrip strength were the primary outcomes of the meta-analysis. The secondary outcomes, related to physical performance, were Short Physical Performance Battery (SPPB), gait speed, and the five-chair-rise test (5CRT). The main results of the meta-analysis show no statistical differences for upper-limb (SMD: 0.56, 95% CI: −0.09, 1.21, $p = 0.09$, I2 = 68%), lower-limb (SMD: 0.00, 95% CI: −0.18, 0.18, $p = 1.0$, I2 = 11%), and handgrip strength (SMD: 0.03, 95% CI: −0.26, 0.32, $p = 0.84$, I2 = 0%) between the RT + PS and the RT alone (or combined with plS). Moreover, no statistical differences were found relating to physical performance. In view of these results, protein supplementation combined with RT does not provide additional benefits compared to RT alone or with plS in healthy elderly adults.

Keywords: elderly; resistance training; protein supplementation; muscle strength; physical performance

Effectiveness of protein supplementation combined with resistance training on muscle strength and physical performance in elderly: A systematic review and meta-analysis.

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ABSTRACT

The aim of this study was to evaluate the effectiveness of the combination of resistance training (RT) and protein supplementation (PS), compared to RT alone or combined with a placebo (plS), in the improvement of muscle strength and physical performance. The search strategy in PubMed, Cochrane Library, and Web of Sciences databases found a total of 294 studies. Once inclusion and exclusion criteria were applied, 16 studies were included for the qualitative analysis. A total of 657 healthy elderly (>60 years) participants were analysed. Finally, 15 articles were included in the quantitative analysis with one being excluded due to issues with data availability. Upper limb, lower limb, and handgrip strength were the primary outcomes of the meta-analysis. The secondary outcomes, related to physical performance, were Short Physical Performance Battery (SPPB), gait speed, and five chair rise test (5CRT). The main results of the meta-analysis showed no statistical differences for the upper limb (SMD: 0.56, 95% CI: -0.09, 1.21, p=0.09, I2=68%), lower limb (SMD: 0.00, 95% CI: -0.18, 0.18, p=1.0, I2=11%), and handgrip strength (SMD: 0.03, 95% CI: -0.26, 0.32, p=0.84, I2=0%) between the RT + PS and the RT alone (or combined with plS). Moreover, no statistical differences were found relating to physical performance. In view of these results, protein supplementation combined with RT does not provide additional benefits compared to RT alone or with plS in healthy elderly adults.

KEYWORDS

elderly; resistance training; protein supplementation; muscle strength; physical performance

1. Introduction

The ageing of the world's population and the physical inactivity of older adults represent a major public health problem [1]. Lower mortality and increasing lifespan have led to a diversification and growth in chronic disease morbidity [2]. Such a trend includes an increased prevalence of aging-related mobility impairments, even with aging in the absence of disease [3]. Moreover, only 27–44% of older U.S. adults meet the World Health Organization’s (WHO) general recommendations for physical activity in adults [1,4]. In fact, individuals who did not meet this criteria have been found to have double the risk of future limitations in functional capacity [5].

Traditionally, sarcopenia has been defined as the muscle mass decrease related to aging [6]. However, the European Working Group on Sarcopenia in Older People (EWGSOP) recently stated that more attention should be given to a reduced muscle strength as the key characteristic to define and identify sarcopenia, with reduced muscle mass and physical performance taken as secondary factors [7]. Sarcopenia has an estimated prevalence of 10% in adults older than 60 years [3,8], rising to 50% in adults older than 80 years [3,8]. Studies show that elderly patients with lower muscle mass and strength have an increased probability of becoming dependent prematurely [9], longer and more frequent hospitalizations [10], and mortality [11], which in turn translates into higher healthcare costs [10].

Resistance training (RT) in the elderly population has been shown as the most useful tool for avoiding sarcopenia [3,12,13]. Moreover, RT alone or combined with other training methodologies has demonstrated to be effective on the development of muscle mass, strength, and physical performance, as well as a decreased risk of fall in the physically frail elderly population [3,14].

Additionally, total protein intake seems to play an important role in sarcopenia [15,16]. However, protein supplementation (PS) alone has shown inconclusive results in its effectiveness to increase muscle mass, strength, and physical performance in sarcopenic population [17,18]. Further studies have shown positive effects of PS on muscle mass when combined with RT in older adults [19,20]. Given the importance of muscle strength and physical performance in the prevention and attenuation of sarcopenia, it is important to analyse whether combined RT and PS protocols are effective in improving these parameters [21].

The aim of this study is to evaluate if the combination of resistance training (RT) and protein supplementation (PS) is more effective than resistance training alone or combined with placebo (plS) in improving muscle strength and physical performance in healthy elderly adults.

2. Materials and Methods

2.1. Protocol and Registration

The study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist [22]. The systematic review and meta-analysis protocol was registered in the Open Sciences Framework platform with the following DOI number: 10.17605/OSF.IO/CMU4R.

2.2. Information Sources and Search

The PICO strategy was taken into account in order to develop an accurate search strategy. The elected population was elderly people; the intervention studied was resistance training (RT) combined with protein supplementation (PS); the comparison chosen was resistance training alone or with placebo supplementation (plS); and the principal outcomes were physical performance (PP) and strength (ST). The search strategy was combined with RCT filters proposed by the Cochrane Collaboration [23]. The keywords used to develop the search are shown and classified by the PICO strategy on Table 1.

PubMed, Cochrane Library, and Web of Science were the databases used in this systematic review and meta-analysis. Moreover, manual searches and lists of references from additional studies were included, and other similar systematic reviews were checked in order to find potential studies that might meet the inclusion criteria. The final search was performed on June 5th, 2020. Table 2 shows the PubMed search strategy. The complete search strategies are available on the Supplementary Appendix S1.

Table 1. Keywords used for the search strategy.

Population	**Intervention**	**Control**	**Outcomes**
Aged	Resistance training	Protein supplementation	Physical fitness
Old people	Strength training	Supplemental	Functionality

	protein	
Elderly		Performance
Aging		Fitness
Older people		Strength
Older adults		Resistance
Old adults		Endurance
Frail		Balance
Senior		Stability
Geriatric		Agility
		Mobility
		Gait
		Speed
		Locomotion

Fall
Falling
Handgrip
SPPB
Tandem
TUG
Timed up and go
Quality of life
Min-mental
Cognition

Table 2. Search Strategy.

PubMed Search Strategy
((((physical fitness OR functionality OR Performance OR Strength OR Resistance OR Endurance OR balance OR stability OR agility OR mobility OR Gait OR Speed OR Locomotion OR fall OR Handgrip OR SPPB OR Tandem OR TUG OR "Timed up and go" OR "quality of life") AND (aged OR "old people" OR "older people" OR "older adults" OR "old adults" OR elderly OR senior OR geriatric OR frail)) AND ((resistance training) OR (strength training))) AND ("protein supplementation" OR "supplemental protein")) AND (((((((((randomized controlled trial [pt]) OR controlled clinical trial [pt]) OR randomized [TiAb]) OR placebo [TiAb]) OR clinical trials as topic [mesh: noexp]) OR randomly [TiAb]) OR trial [Ti])) NOT ((animals [mh] NOT humans [mh]))))

2.3. Eligibility Criteria and Study Selection

Studies were included if they met the following criteria: 1) randomized controlled trial (RCT) study design, 2) adults aged >60, 3) healthy participants with or without sarcopenia condition, 4) intervention group with resistance training combined with protein supplementation, 5) comparison group with resistance training combined with placebo supplementation or no supplementation, 6) physical performance or strength as outcome, and 7) English language.

Studies were excluded if 1) sample were hospitalized or post-surgery participants, 2) sample with diabetes, cancer, cardiovascular disease, or other several acute/chronic condition, 3) other supplementation as vitamins, and 4) resistance training duration less than 8 weeks.

Two authors (NL and LLL) independently screened titles, abstracts, and full text for potential inclusion. APB was consulted in case of discrepancy. Inter-rater agreement was assessed by using Cohen's Kappa index [24].

2.4. Data Collection Process

For each study included in this systematic review the following data was extracted: 1) author's last name, 2) year of publication, 3) sample size, 4) duration and frequency of the resistance training protocol, 5) type and dosage of protein supplementation, 6) control group protocol, 7) outcomes, and 8) main results.

2.5. Outcomes

The present systematic review and meta-analysis focused on two main outcomes: strength and physical performance. The assessment of the strength capacity was focused on those tests of which goal was to determine the ability to generate high forces against large resistances. The assessment of physical performance included other speed or agility tests with greater coordinative demands.2.6. Risk of Bias of Individual Studies

The Risk of Bias 2 tool (RoB 2) [25] from the Cochrane Collaboration and Physiotherapy Evidence Database (PEDro) scale [26] were used to assess the methodological quality and risk of bias of the randomized controlled studies included on this systematic review and meta-analysis.

The Risk of Bias 2 tool [25] from the Cochrane Collaboration is a domain-based evaluation that classifies seven domains from each randomized controlled trial into “low”, “unclear” or “high” risk of bias. The seven domains are based on publication bias (sequence generation and allocation sequence concealment), performance bias (blinding participants and personnel), detection bias (blinding outcome assessor), attrition bias (incomplete data), reporting bias (selecting outcome reporting), and other bias (e.g. sample size).

The PEDro scale [26] is an 11-item scale that relates the external validity (item 1), the internal validity (items 2-9), and the applicability or generalizability (items 10-11). One point is awarded if the criterion is clearly satisfied and thus, 11 points is the maximum score showing the highest methodological quality of a randomized controlled trial.

2.7. Statistical Analyses

The present meta-analysis was carried out using the RevMan Manager 5.3 software (The Cochrane Collaboration, 2012). The sample size, means, and standard deviations (SD) for each variable were introduced in the software. If necessary, SD was calculated by standard error or confidence interval. All outcomes were continuous. If studies used different measuring tools, the chosen measure of effect size was Standard Mean Difference (SMD). On the other hand, if studies used the same measuring tool, Mean Difference (MD) was chosen as the effect size measure. An overall effect size with a 95% interval confidence (CI) was calculated. When studies did not report specific data (e.g. only graphs) an email was sent to the corresponding author asking for the missing data. If no response was received, the study was removed from the meta-analysis.

The SMD or MD of each outcome was calculated using a random-effects model (DerSimonian-Laird approach [27]). Heterogeneity across studies was evaluated by I2 statistics. Heterogeneity was classified as “small”, “moderate”, or “high” if I2 was <25%, 25%-75%, and >75%, respectively, as Higgins et al. proposed [28]. The individual influence of each study on the overall result was analysed removing each study once. Funnel plot visual interpretation was performed for outcomes with more than ten studies.

3. Results

3.1. Search strategy

The search strategy found 294 studies (PubMed: 95; Cochrane Library: 105; Web of Science: 94). An additional study was included after performing the manual search. A total of 128 studies were excluded after checking and removing duplicates. A hundred and sixty-seven studies were initially considered to be included.

3.2. Study selection

Firstly, the titles and abstracts of all included studies were screened, and 144 were excluded after this preliminary filter. Secondly, full text screening was carried out and 16 studies met the inclusion criteria for the qualitative analysis. One study was removed from the meta-analysis for not presenting the required data and after receiving no response from the corresponding author. Finally, 15 articles were included in the quantitative synthesis.

Analysis of Cohen’s Kappa index showed a k=0.83 categorized as “almost perfect” agreement [24]. PRISMA flow chart with detailed study selection is displayed in Figure 1.

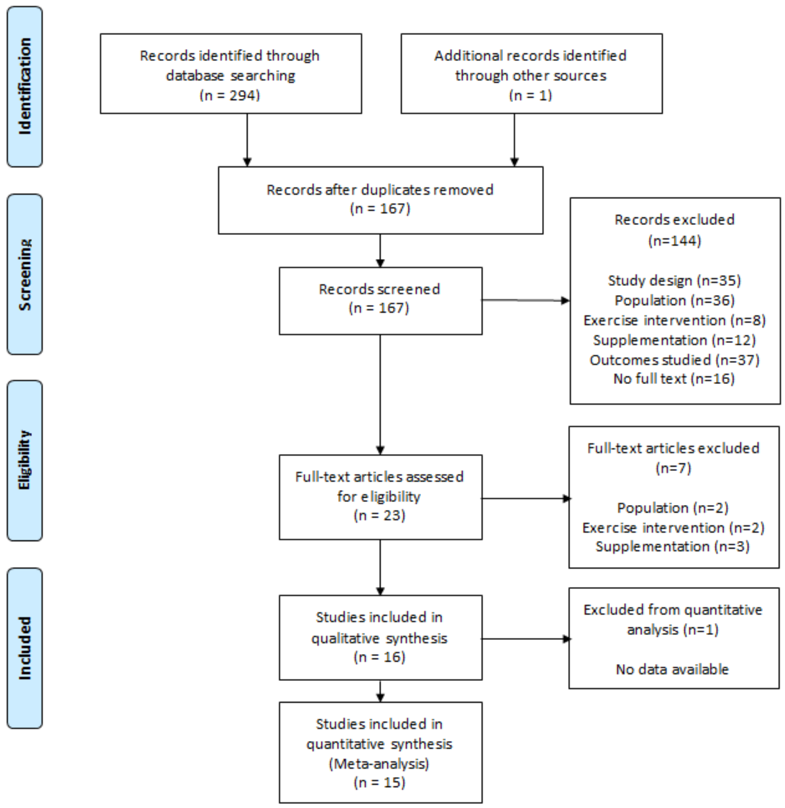

Figure 1. Search PRISMA flow diagram.

3.3. Study Characteristics

The characteristics of the included studies are summarized in Table 3. The 16 studies included in this systematic review involved a total of 657 elderly individuals. Four studies included only women while five studies included only men. The other seven studies included both male and female participants. Sample sizes across studies ranged from 11 [29] to 141 [30].

Studies included in this systematic review involved participants from three continents. Two studies were from Asia, two studies were carried out in North America, three in South America, and nine studies in Europe.

Resistance training interventions had a duration of 12 weeks in most studies (n=11) and the most common frequency was 3 times/week (n=11). Whey protein supplementation was the most common across studies (n=12). Fourteen studies assessed either lower-body or upper-body strength and 11 studies assessed function outcomes.

The control group of 14 studies received the same resistance training program plus a placebo supplementation. The remaining two studies had a control group receiving the same RT program without placebo supplementation. Full additional characteristics of the sample and the resistance training are available on Supplementary Appendix S2 and S3.

Table 3. Characteristics of the studies included in the qualitative analysis.

Study	Population		RT Intervention	PS Intervention		CG	Outcomes	Main Results
	N (EG/CG)	Gender (M/F)	Duration x Frequency	Type	Amount (g/d or g/s)			
Amasene, 2019	28 (15/13)	14/14	12 w x 2 s/w	Whey (+ Leucine enriched)	20g (+3g)/s	RT + plS	PP	ND PP
Arnarson, 2013	141 (76/66)	NR	12 w x 3 s/w	Whey	20g/s	RT + plS	ST, PP	ND LLS ND PP
Candow 2008	22 (10/12)	20/0	10 w x 3 s/w	Whey (+ Creatin)	Protein: $0.3g{\cdot}kg^{-1}$ Creatin: $0.1g{\cdot}kg^{-1}$	RT + plS	ST	↑ ULS ND LLS
Holwerda, 2018	40 (21/19)	40/0	12 w x 3 s/w	Whey (+ Leucine enriched)	21g/d	RT + plS	ST, PP	ND LLS ND SPPB

Krause, 2019	21 (11/10)	12/9	12 w x 3 s/w	Whey	0.165 $g \cdot kg^{-1}$	RT + plS	PP	ND PP
Leenders, 2013	53 (27/26)	29/24	24 w x 3 s/w	Whey + Casein	3g + 12g/d	RT + plS	ST, PP	ND LLS ND 5CRT ND HS
Mori, 2018	50 (25/25)	0/50	24 w x 2 s/w	Whey	25g/s	RT	ST, PP	ND LLS ND HS ND GS
Nabuco, 2018	44 (21/23)	0/44	12 w x 3 s/w	Whey	35g/s	RT + plS	ST, PP	↑ ST ↑ PP

Table 3. Cont.

Study	Population		RT Intervention	PS Intervention		CG	Outcomes	Main Results
	N (EG/CG)	Gender (M/F)	Duration x Frequency	Type	Amount (g/d or g/s)			
Nabuco, 2019	26 (13/13)	0/26	12 w x 3 s/w	Whey	35g/s	RT + plS	ST, PP	ND ST ND PP
Stragier S, 2016	25 (12/13)	11/14	24 w x 2 s/w	Leucine	27.6g/d	RT + plS	ST	ND LLS
Sugihara, 2018	31 (15/16)	0/31	12 w x 3 s/w	Whey	35g/s	RT + plS	ST	↑ ST
Tieland, 2012	53 (26/27)	NR	24 w x 2 s/w	Whey	15g/d	RT + plS	ST, PP	ND LLS ND HS ND SPPB ND GS 5CRT
Trabal, 2015	11 (7/4)	NR	12 w x 4 s/w	Leucine	10g/d	RT + plS	ST, PP	↑ LLS ↑ TUG

								ND 5CRT
Verdijk, 2009	26 (13/13)	26/0	12 w x 3 s/w	Casein	20g/s	RT + plS	ST	ND LLS
Villanueva, 2014	14 (7/7)	14/0	12 w x 3 s/w	Whey (+ Creatin)	35g/d	RT	ST, PP	ND ULS ND LLS ND PP
Zdziebli k D, 2015	53 (26/27)	53/0	12 w x 3 s/w	Collagen peptides	15g/d	RT + plS	ST	↑ LLS

EG: Experimental group; CG: Control group; RT: Resistance Training; PS: Protein Supplementation; plS: Placebo Supplementation; ND: No significant differences; ↑: Significant increase for EG; ↓: Significant decrease for EG; w: week; d: day; s: session; ST: Strength; LLS: Lower Limb Strength; ULS: Upper Limb Strength; HS: Handgrip Strength; PP: Physical Performance; SPPB: Short Physical Performance Battery, GS: Gait Speed, 5CRT: 5 Chair Rise Test; TUG: Timed Up and Go Test; NR: No reported.

3.4. Risk of Bias Assessment

The methodological quality assessment by PEDro scale revealed a high quality across studies included in this systematic review. The average PEDro scale score was 8.5 points out of 11 (Table 4).

The RoB 2 tool summary and graph are shown in Figures 2 and 3. Nine studies (56%) had at least four domains with “low risk”. Three studies (18%) had two or more domains as “high risk”.

Table 4. PEDro scale.

Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Total**
Amasene, 2019	X	X	X	X	X				X	X	X	8
Arnarson, 2013	X	X	X	X	X	X		X		X	X	9
Candow 2008	X	X	X	X	X	X		X		X	X	9
Holwerda, 2018	X	X	X	X	X	X		X		X	X	9
Krause, 2019	X	X	X	X	X			X	X	X	X	9
Leenders, 2013	X	X	X	X	X	X		X		X	X	9
Mori, 2018	X	X	X	X	X			X		X	X	8
Nabuco, 2018	X	X	X	X	X	X		X	X	X	X	10
Nabuco, 2019	X	X	X	X	X	X		X		X	X	9
Stragier S, 2016	X	X		X						X	X	5
Sugihara, 2018	X	X	X	X	X	X		X	X	X	X	10
Tieland, 2012	X	X	X	X	X	X		X	X	X	X	10
Trabal, 2015	X	X	X	X	X	X				X	X	8
Verdijk, 2009	X	X	X	X			X	X		X	X	8
Villanueva, 2014	X	X	X	X				X		X	X	7

Zdzieblik D, 2015	X	X	X	X	X		X	X		X	X	9
Average												8.5

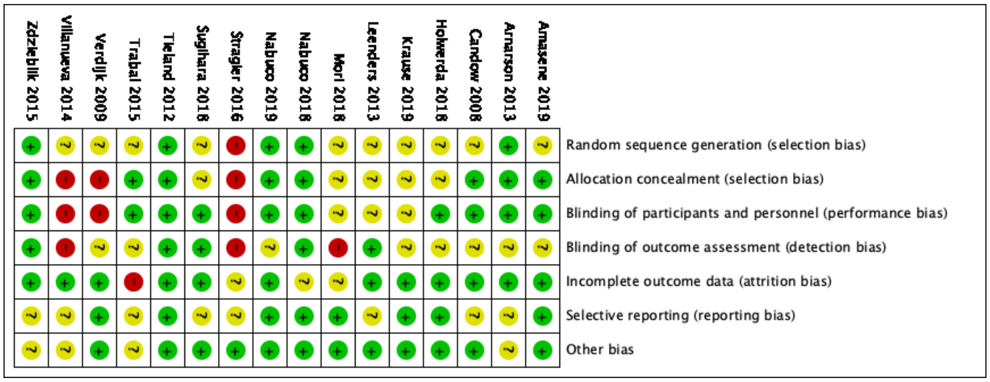

Figure 2. Risk of bias summary.

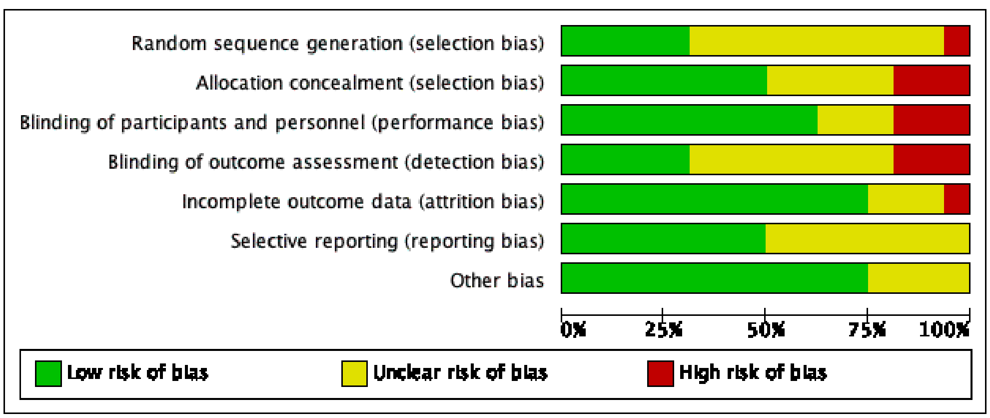

Figure 3. Risk of bias graph.

3.5. Outcomes

The primary outcome assessed was strength (ST). It was often measured by using repetition maximum (RM) during leg extension for the lower extremity assessment, RM during chest press for the upper extremity assessment, and handgrip strength (HS). The secondary outcome was physical performance (PP). The main tests used to assess physical performance involved gait speed (GS), Short Physical Performance Battery (SPPB), and the five-chair rise test (5CRT).

3.5.1. Lower limb strength (LLS)

Fourteen studies provided data about changes in lower extremity strength. Thirteen of them assessed maximal quadriceps strength using a leg extension test (n=12) or a leg press (n=1). Among the 13 studies, nine followed the 1-RM method, two used an isometric dynamometer and two an isokinetic dynamometer. One study assessed the maximal voluntary contraction (MVC) of the plantar flexor muscles using surface electromyography. These studies involve a total sample size of 589 participants (298 in the protein supplementation + resistance training group and 291 in the resistance training group).

The overall standard mean difference was 0.00 with a 95% confidence interval of [-0.18, 0.18] and an overall effect p=1.0. The heterogeneity showed by I2 statistic was low (I2=11%). Figure 4 shows the forest plot for lower limb strength. Visual interpretation of the funnel plot reveals no evidence of publication bias for this outcome.

	PS + RT			RT				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Arnarson 2013	56.5	59.4	75	53.8	51.8	66	20.2%	0.05 [−0.28, 0.38]
Candow 2008	20	6	10	21	5	12	4.2%	−0.18 [−1.02, 0.67]
Holwerda 2018	102	4	21	105	4	19	6.8%	−0.74 [−1.38, −0.09]
Leenders 2013	110.12	26.75	27	111.53	22.83	26	9.3%	−0.06 [−0.59, 0.48]
Mori 2018	26.4	5.5	25	27.8	4.3	25	8.8%	−0.28 [−0.84, 0.28]
Nabuco 2018	59	12	21	56	13	23	7.9%	0.24 [−0.36, 0.83]
Nabuco 2019	51.8	10.9	13	53.4	9.4	13	4.9%	−0.15 [−0.92, 0.62]
Stragier 2016	115.8	28	12	113.7	38.3	13	4.7%	0.06 [−0.72, 0.84]
Sugihara 2018	57.2	10.9	15	55.1	13.1	16	5.8%	0.17 [−0.54, 0.88]
Tieland 2012	76.8	17.3306	26	79.3	17.948	27	9.3%	−0.14 [−0.68, 0.40]
Trabal 2015	12.48	4.8153	7	6	4.6	4	1.6%	1.25 [−0.14, 2.64]
Verdijk 2009	115	5	13	111	5	13	4.5%	0.77 [−0.03, 1.58]
Villanueva 2014	363.2	131.4	7	327.7	87.3	7	2.7%	0.30 [−0.76, 1.35]
Zdzieblik 2015	140	28.3	26	139	27.4	27	9.3%	0.04 [−0.50, 0.57]
Total (95% CI)			**298**			**291**	**100.0%**	**−0.00 [−0.18, 0.18]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 14.53$, df = 13 (P = 0.34); $I^2 = 11\%$
Test for overall effect: Z = 0.01 (P = 1.00)

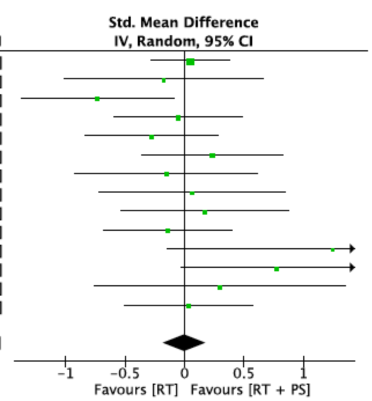

Figure 4. Impact of RT + PS on lower limb strength.

3.5.2. Upper limb strength (ULS)

Five studies provide data about changes in upper extremity strength. The test used for this variable was a chest/bench press test. All studies assessed the maximal strength using de 1-RM method. A total of 66 participants were included in the intervention group (protein supplementation + resistance training) and 71 participants were included in the control group (only resistance training).

The intervention and control groups did not differ in upper limb strength with an overall standard mean difference of 0.56 with a 95% confidence interval of [-0.09, 1.21] and an overall effect p=0.09. The I2 statistic revealed a moderate heterogeneity across studies (68%) (Figure 5). To investigate this factor, all studies were removed once from the analysis. When Candow et al. [32] study was removed, the heterogeneity was 0%.

	PS + RT			RT				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Candow 2008	19	4	10	9	4	12	15.5%	2.41 [1.26, 3.55]
Nabuco 2018	48	10	21	45	8	23	24.1%	0.33 [−0.27, 0.92]
Nabuco 2019	44.8	8.6	13	42.8	7.1	13	21.2%	0.25 [−0.53, 1.02]
Sugihara 2018	47	8.8	15	45.2	7.4	16	22.3%	0.22 [−0.49, 0.92]
Villanueva 2014	72.7	15	7	71.8	30.5	7	16.9%	0.04 [−1.01, 1.08]
Total (95% CI)			**66**			**71**	**100.0%**	**0.56 [−0.09, 1.21]**

Heterogeneity: $Tau^2 = 0.36$; $Chi^2 = 12.58$, df = 4 (P = 0.01); $I^2 = 68\%$
Test for overall effect: Z = 1.69 (P = 0.09)

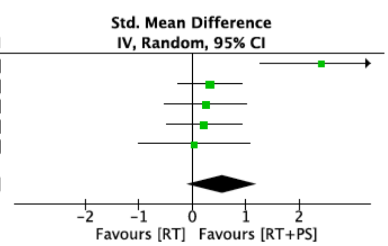

Figure 5. Impact of RT + PS on upper limb strength.

3.5.3. Handgrip strength (HS)

Only four studies provided sufficient data about handgrip strength involving 93 participants for the intervention group and 89 participants for the control group. The overall standard mean difference was 0.03 with a 95% confidence interval [-0.26, 0.32] and an overall effect p=0.84. The heterogeneity was I2=0% (Figure 6).

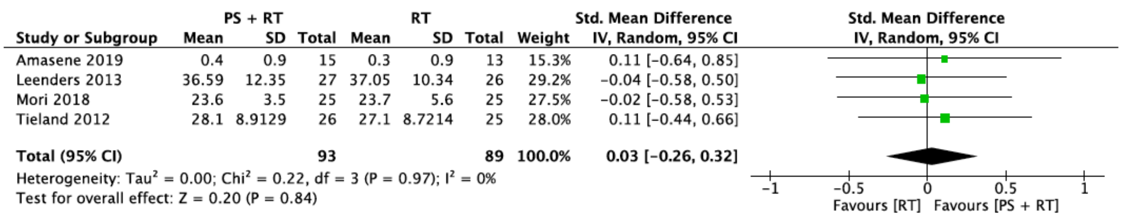

Figure 6. Impact of RT + PS on handgrip strength.

3.5.4. Gait Speed (GS)

Five studies evaluated the physical performance by assessing participant’s gait speed. Intervention group and control group sample sizes were 92 and 90 participants, respectively.

Two studies evaluated gait speed in meters per second. However, three studies assessed it as the seconds to complete 10 meters. Thus, the directionality of this data had to be opposed in the meta-analysis.

The overall standard mean difference was 0.11 with a 95% confidence interval [-0.18, 0.40] and an overall effect of p=0.45. The heterogeneity across studies was 0% based on I2 statistics (Figure 7).

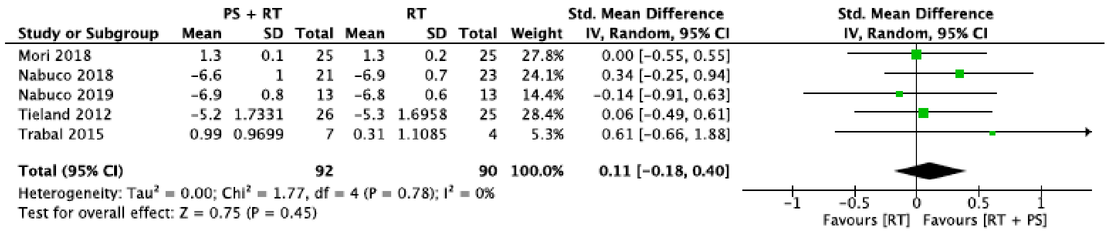

Figure 7. Impact of RT + PS on gait speed.

3.5.5. Short Physical Performance Battery (SPPB)

Three studies were included in this outcome analysis involving 119 participants (62 intervention group and 57 control group). All studies used the same scale, so the Mean Difference was used as the effect size measure.

Protein supplementation plus resistance training group and resistance training group did not differ in terms of SPPB. The overall mean difference was 0.21 with a 95% confidence interval [-0.44, 0.85] and an overall effect of p=0.53. Analysis by I2 statistic revealed a moderate heterogeneity (I2=50%). Removing the study from Amasene et al. [31] or the one from Holwerda et al. [33], the heterogeneity decreased to I2=0% (Figure 8).

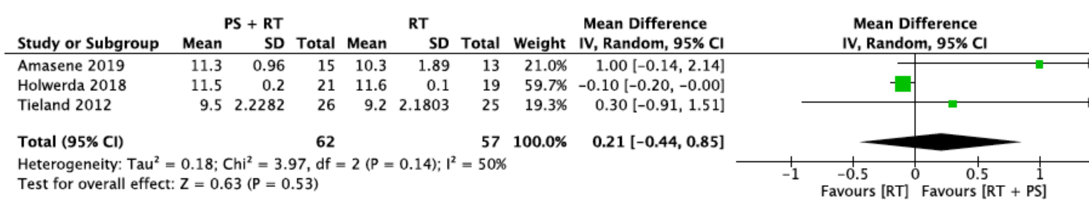

Figure 8. Impact of RT + PS on Short Physical Performance Battery (SPPB).

3.5.6. Five chair rise test (5CRT)

Six studies measured physical performance by the five-chair rise test. This analysis involved 108 participants in the intervention group and 104 participants in the control group. Trabal et al. [29] only provided data of the change from baseline, so higher values implied better results. However, five studies measured it as the necessary time to achieve five chair rises with higher values implying worse results. Therefore, the data directions of these studies needed to be opposed for the meta-analysis.

The overall standard mean difference was 0.16 with a 95% confidence interval [-0.12, 0.43] and overall effect of p=0.26. The heterogeneity across the studies was I2=0 (Figure 9).

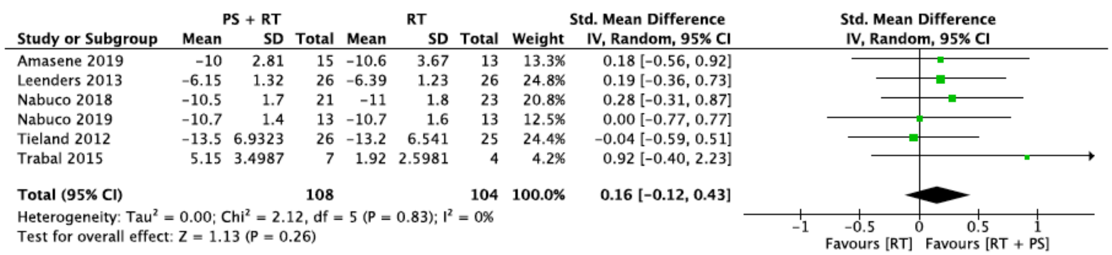

Figure 9. Impact of RT + PS on five chair rise test (5CRT).

Finally, a subgroup analysis regarding on sarcopenic or healthy elderly participants was performed in order to assess differences with overall sample results. However, all forest plots indicated no statistical subgroup differences (P<0.05). Forest plot with detailed information about this analysis are available on the Supplementary Appendix S4

Complete sensitivity analysis is also available in the Supplementary Appendix S5.

4. Discussion

The present article aims to summarize the effects of a RT intervention combined with PS compared to a RT intervention alone or combined with placebo supplementation on strength and physical performance in the healthy elderly population. This systematic review summarizes findings from a total of 16 studies and including a total of 657 participants.

To our knowledge, this is the first meta-analysis that compares RT plus PS with RT alone or plus placebo supplementation in a healthy elderly population. Notably, there are similar previous studies that compared different populations, such as younger population [45,46] or elderly hospitalized people [47]; included a combination of other supplements, such as vitamin 3, omega-3, or a dietary intake modification [48–52]; or studied other outcomes related to body composition [53,54].

In view of the results, our meta-analysis shows no statistical differences between RT in combination with PS compared with RT alone or combined with placebo on upper and lower limb strength, handgrip strength, gait speed, and functional tests SPPB and 5CRT.

4.1. Muscle Strength

Handgrip strength is a simple and inexpensive way to assess muscle strength [55], and it has been established as a reliable tool to predict increased functional limitations, quality of life, and death [56,57]. Moreover, handgrip strength has a moderate correlation with the strength of other parts of the body [7]. In fact, chest and leg press exercises are also used for the assessment of muscle strength in the elderly population [58].

Our findings suggest that protein supplementation does not provide any greater benefit when compared to RT alone or combined with placebo in terms of muscle strength improvements in both lower and upper limbs and handgrip strength in healthy elderly adults. These results agree with previous meta-analyses conducted by Ten Haaf et al. [47], Finger et al. [50], and Morton et al. [59], but differ from Hou et al. [60] and Liao et al. [19].

We believe that the difference between our findings and these studies lies in that Hou et al. [60] and Liao et al. [19] included other supplements such as vitamin D, and their study populations were aged >50 years [60] or included hospitalized people [19]. In that sense, it could be hypothesized that PS might only provide additional benefits to RT in frail people, who are characterised by greater losses of muscle mass which may limit muscle strength development.

It is important to note that heterogeneity across studies was low for lower limb strength (I2=11%) and handgrip strength (I2=0%), but moderate for upper limb strength (I2=68%). Heterogeneity for upper limb strength could be explained by the study of Candow et al. [32]. The heterogeneity was 0% when it was removed. The study design proposed by Candow et al. [32] is the only one including a ST program shorter than 12 weeks, which is the duration recommended by the National Strength and Conditioning Association (NSCA) [3]. This study notably favours RT + PS with a standard mean difference [95%CI] of 2.41 [1.26, 3.55]. It is difficult to provide with consistent evidence-based explanations given the large heterogeneity of the results. It could be possible that the effects of the PS on the upper limb muscle strength appear in a shorter term (<12 weeks) and favour the combination RT + PS. However, as the other included studies have a longer duration (>12 weeks), the effects of the PS might be underestimated.

4.2. Physical Performance

Apart from strength, physical performance assesses the whole-body function related to locomotion and the individual's health status [7,13]. Some of the most relevant functional tests are SPPB [61,62], Gait Speed [63–65], and 5CRT [66,67].

As suggested by a previous meta-analysis conducted by Ten Haaf et al. [47] and Hou et al. [60], our results also show that PS combined with RT is not more effective than RT alone or combined with placebo in developing physical performance improvement in healthy elderly adults. In contrast, when studying a frailer population (hospitalized, institutionalized, or community-dwelling elderly individuals with a high risk of sarcopenia or frailty and physical limitations), the results from Liao et al. [19] showed significant improvements in the RT + PS group. These findings suggest that frail people who have some physical impairments could benefit from protein supplementation, but not in the case of healthy people with no severe physical limitations.

4.3. Protein Supplementation

Current recommendations for daily protein intake range from 1.2 to 1.5g/kg body weight/day for elderly active population [68,69]. These amounts can be achieved through diet or through protein supplementation. To date, there is no general recommendation on the appropriate protein supplementation dose, since it depends on the body composition of each individual, as well as on their physical fitness and health conditions. However, some studies indicate that the dose could be between 25-30g of protein [70]. Following these data, in at least 8 of the studies included in this review, the supplementation dose is less than 25g, so its benefits may not be reflected.

In general, our findings support the idea that resistance training is one of the most effective strategies to prevent or delay frailty condition in elderly population.

Finally, the absence of additional benefits of PS when combined to RT suggests that we should rethink if it is necessary to supplement with protein every elderly people without taking into account their fitness or their health status.

This meta-analysis has some limitations, mainly related to the heterogeneous characteristics (intensity, frequency, volume etc.), and duration of the resistance training programs, the different types and doses of protein intake, and the diversity of the methods used to assess muscle strength and physical performance. Moreover, a longer follow-up may have been interesting to analyse if differences are seen in the long term.

5. Conclusions

In view of our results, there is not sufficient evidence to support the use of protein supplementation when combined with resistance training in healthy elderly adults for improving muscle strength and physical performance. Protein supplementation combined with RT does not provide additional benefits compared to RT alone. Future primary studies are needed to analyse the different protocols of protein supplementation. Furthermore, studies with longer follow-up periods should be conducted in order to analyse possible differences over time.

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results. N.L.L., L.LL.A. and J.R.S. wrote the article. C.L.C., V.G.R., C.H.G., B.M.P. and A.P.B. reviewed and verified the paper. As the contact author, A.P.B. has overall responsibility for the review. All authors have read and agreed to the published version of the manuscript.

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Supplementary Appendix S1: Complete literature search

PubMed Search Formula

#1 (aged [mh] OR aged OR "old people" OR "older people" OR "older adults" OR "old adults" OR elderly OR senior OR geriatric OR frail)

#2 (resistance training [mh] OR resistance training OR strength training)

#3 ("protein supplementation" OR "supplemental protein")

#4 (physical fitness [mh] OR physical fitness OR functionality OR Performance OR Strength OR Resistance OR Endurance OR balance OR stability OR agility OR mobility OR Gait OR Speed OR Locomotion OR fall OR Handgrip OR SPPB OR Tandem OR TUG OR "Timed up and go" OR "quality of life")

#5 (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [TiAb]) OR placebo [TiAb] OR clinical trials as topic [mesh: noexp] OR randomly [TiAb]) OR trial [Ti]) NOT (animals [mh] NOT humans [mh])

#6 #1 AND #2 AND #3 AND #4 AND #5

Results: 95

Date: 18/05/2020

Cochrane Library Search Formula

#1 MeSH descriptor: [Aged] explode all trees

#2 aged OR "old people" OR "older people" OR "older adults" OR "old adults" OR elderly OR senior OR geriatric OR frail

#3 #1 OR #2

#4 "resistance training" OR "strength training"

#5 "protein supplementation" OR "supplemental protein"

#6 MeSH descriptor: [Physical Fitness] explode all trees

#7 physical fitness OR functionality OR Performance OR Strength OR Resistance OR Endurance OR balance OR stability OR agility OR mobility OR Gait OR Speed OR Locomotion OR fall OR Handgrip OR SPPB OR Tandem OR TUG OR "Timed up and go" OR "quality of life"

#8 #6 OR #7

#9 #3 AND #4 AND #5 AND #8

Results: 105

Date: 18/05/2020

Web of Science Search Formula

#1 ALL=(aged OR “old people” OR “older people” OR “older adults” OR “old adults” OR elderly OR senior OR geriatric OR frail)

#2 ALL=(“resistance training” OR “strength training”)

#3 ALL=(“protein supplementation” OR supplemental protein”

#4 ALL=(physical fitness OR functionality OR Performance OR Strength OR Resistance OR Endurance OR balance OR stability OR agility OR mobility OR Gait OR Speed OR Locomotion OR fall OR Handgrip OR SPPB OR Tandem OR TUG OR "Timed up and go" OR "quality of life")

#5 TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*)

#6 (TS=#1 AND #2 AND #3 AND #4 AND #5)

Results: 94

Date: 18/05/2020

Supplementary Appendix S2: Additional characteristics of the resistance training protocols

Supplementary Table 1. Additional characteristics of the resistance training protocols

Study	Type of exercise	Volume load progression*		Number of exercises	Single joint-multi joint exercises	Mean rate of volume load increase	Proximity to failure	Volume split/body part
		Baseline volume load	Final volume load					
Amasene, 2019	UB and LB resistance training + dynamic balance exercises	96 x NS x 50-65	168 x NS x 70	6	4-2	NS	NS	NS
Arnarson, 2013	UB and LB resistance training	NS x NS x 60	990 x 6-8 x 75-80	10	7-3	5-10%/week	6-8 RM	NS
Candow 2008	UB and LB resistance training	NS	810 x 10 x 70	9	5-4	NS	10-RM	NS
Holwerda, 2018	UB and LB resistance	144 x 8-10 x 70-80	288 x 10 x 80	6	1-5	NS	10-RM	NS

	training							
Krause, 2019	UB and LB bodyweight and elastic bands resistance training	270 x 8-12 x NS	990 x 10-14 x NS	10	3-7	NS	NS	NS
Leenders, 2013	UB and LB resistance training	216 x 8-15 x 60-75	1200 x 8 x 75-80	8	3-5	NS	8-RM	LB exercises: 480 x 8 x 75-80 UB exercises: 720 x 8 x 75-80
Mori, 2018	UB and LB bodyweight and elastic bands resistance training	NS	NS x NS x 50-70	7	2-5	NS	NS	NS
Nabuco, 2018	UB and LB resistance training	576 x 10 x NS	576 x 8-12 x NS	8	5-3	NS	8-12 RM	NS
Nabuco, 2019	UB and LB resistance training	576 x 10 x NS	576 x 8-12 x NS	8	5-3	2 to 5 % for UB exercises	8-12 RM	NS

						5 to 10% for LB exercises		
Stragier S, 2016	UB and LB resistance training	NS x 10 x NS	NS x 10 x NS	NS	NS	NS	10 RM	NS
Sugihara, 2018	UB and LB resistance training	576 x 8-12 x NS	864 x 8-12 x NS	8	5-3	2 to 5 % for UB exercises 5 to 10% for LB exercises	8-12 RM	NS
Tieland, 2012	UB and LB resistance training	NS x 10-15 x 50	NS x 8-10 x 75	6	1-5	NS	NS	NS
Trabal, 2015	UB and LB resistance training + balance exercises	NS	324 x 8 x NS	9	6-3	NS	NS	NS
Verdijk, 2009	LB resistance training	96 x 8-15 x 60-75	96 x 8 x 75-80	2	1-1	NS	8 RM	NS

Villanueva, 2014	UB and LB resistance training	NS	NS x 3-12 x 70	7	1-6	NS	Close but not to failure	NS
Zdzieblik D, 2015	UB and LB resistance training	NS	NS	NS	NS	NS	NS	NS

* Volume load expressed as number of sets x number of repetitions x %1RM.

NS: not specified; RM: repetition maximum; LB: lower-body; UB: upper-body

Supplementary Appendix S3. Additional sample characteristics

Supplementary Table 2. Additional sample characteristics

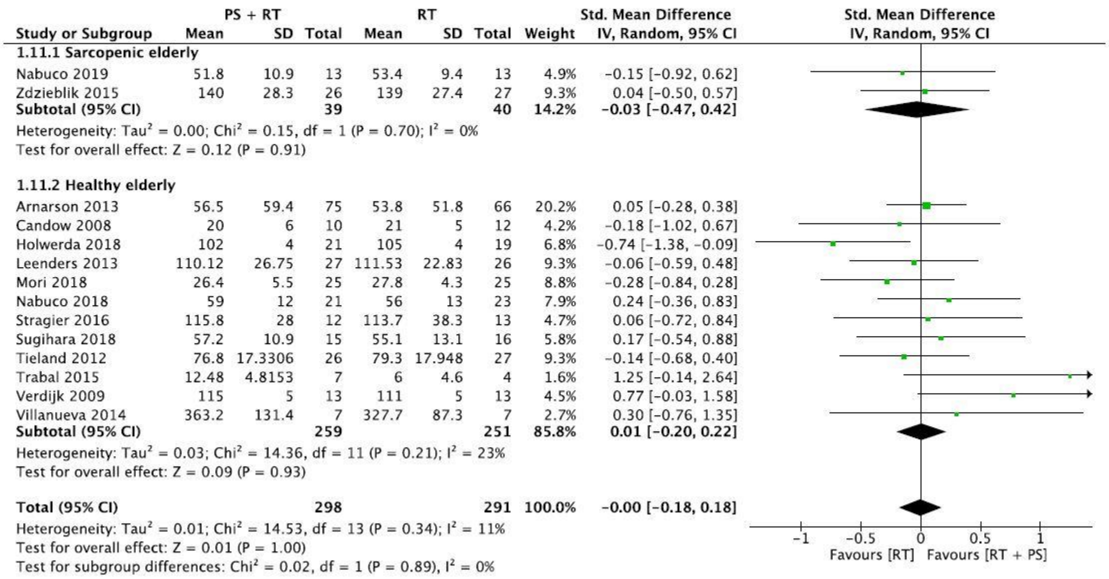
Study	Eating habits of the participants		Overall protein intake		Proportion of sarcopenic individuals
	Protein group	**Placebo group**	**Protein group**	**Placebo group**	
Amasene, 2019	0% malnourished and 27% at risk of malnutrition according to MNA scores	7.7% malnourished and 61.5% at risk of malnutrition according to MNA scores	NS	NS	All sarcopenic
Arnarson, 2013	NS	NS	Baseline: 1.00±0.3 g/kg/day Endpoint: 1.06±0.2 g/kg/day	Baseline: 0.92±0.3 g/kg/day Endpoint: 0.89±0.2 g/kg/day	NS
Candow 2008	No difference between groups following the Interactive Healthy Eating Index		Baseline: 103±9 g/day Endpoint: 104±9 g/day	Baseline: 92±6 g/day Endpoint: 101±9 g/day	Healthy
Holwerda, 2018	Significant increase in total energy intake, Vitamin D and carbohydrate intake pre-post intervention.	Significant increase in total energy intake and carbohydrate intake pre-post intervention.	Baseline: 87±3 g/day Endpoint: 111±3 g/day	Baseline: 93±4 g/day Endpoint: 94±4 g/day	Healthy
Krause, 2019	NS	NS	NS	NS	Healthy
Leenders, 2013	No difference between groups in total energy intake or macronutrient composition.		Men: Baseline: 1.1±0.1 g/kg/day Endpoint: 1.0±0.1 g/kg/day		Healthy

			Women: Baseline: 1.2±0.1 g/kg/day Endpoint: 1.2±0.1 g/kg/day		
Mori, 2018	No difference between groups in total energy intake or macronutrient composition.		Baseline: 1.3±0.0 g/kg/day Endpoint: 1.4±0.0 g/kg/day	Baseline: 1.3±0.0 g/kg/day Endpoint: 1.4±0.1 g/kg/day	NS
Nabuco, 2018	No difference between groups in total energy intake or macronutrient composition.		Baseline: 0.9±0.2 g/kg/day Endpoint: 1.4±0.3 g/kg/day	Baseline: 0.95±0.3 g/kg/day Endpoint: 1±0.3 g/kg/day	NS
Nabuco, 2019	No difference between groups in total energy intake or macronutrient composition.		(Without supplementation) Baseline: 0.9±0.4 g/kg/day Endpoint: 1±0.2 g/kg/day	(Without supplementation) Baseline: 1.0±0.3 g/kg/day Endpoint: 1.0±0.2 g/kg/day	All sarcopenic and obese
Stragier S, 2016	NS		Baseline: NS Endpoint: 1.2±0.3 g/kg/day	Baseline: NS Endpoint: 1.1±0.3 g/kg/day	Healthy
Sugihara, 2018	Significantly higher total energy intake pre-post intervention.	Significantly higher carbohydrate, protein and total energy intake pre-post intervention	Baseline: 0.9±0.1 g/kg/day Endpoint: 1.4±0.1 g/kg/day	Baseline: 0.8±0.1 g/kg/day Endpoint: 0.9±0.1 g/kg/day	NS
Tieland, 2012	No difference between groups in total energy intake or macronutrient composition.		Baseline: 1.0±0.1 g/kg/day Endpoint: 1.3±0.3 g/kg/day	Baseline: 1.0±0.1 g/kg/day Endpoint: 0.9±0.1 g/kg/day	Healthy but frail
Trabal, 2015	No difference between groups in total energy intake or macronutrient composition.		Baseline: 1.3 g/kg/day 4-week follow-up: 1.3 g/kg/day Endpoint: NS	Baseline: 1.2 g/kg/day 4-week follow-up: 1.4 g/kg/day Endpoint: NS	NS
Verdijk, 2009	No difference between groups in total energy intake or macronutrient composition.		(Without supplementation) Baseline: 1.1±0.1 g/kg/day	(Without supplementation) Baseline: 1.1±0.1 g/kg/day	Healthy

		Endpoint: 1.1±0.1 g/kg/day	Endpoint: 1.1±0.1 g/kg/day	
Villanueva, 2014	No difference between groups in total energy intake or macronutrient composition.	NS	NS	Healthy
Zdzieblik D, 2015	No difference between groups in total energy intake or macronutrient composition.	NS	NS	Sarcopenic

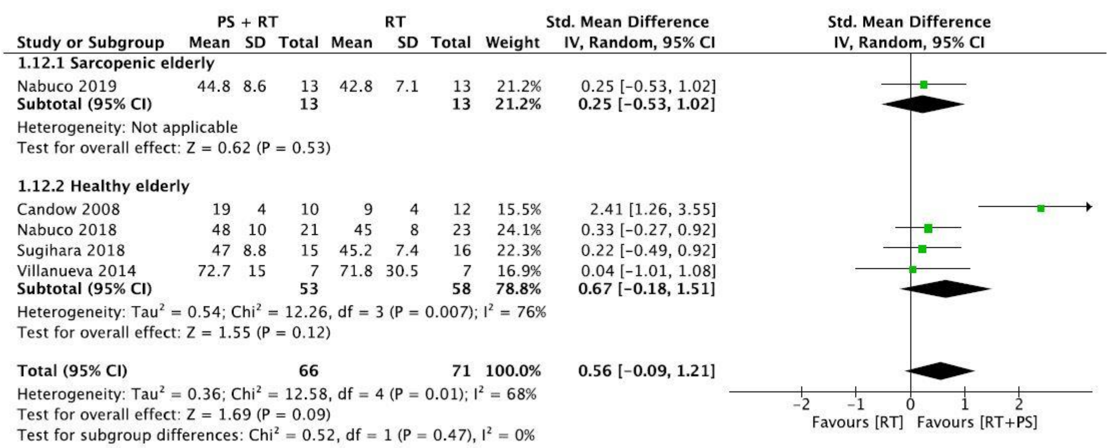
MNA: mini nutritional assessment; NS: non specified.

Supplementary Appendix S4. Subgroup Analysis by Sarcopenia Condition



Study or Subgroup	PS + RT Mean	PS + RT SD	PS + RT Total	RT Mean	RT SD	RT Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.11.1 Sarcopenic elderly								
Nabuco 2019	51.8	10.9	13	53.4	9.4	13	4.9%	−0.15 [−0.92, 0.62]
Zdzieblik 2015	140	28.3	26	139	27.4	27	9.3%	0.04 [−0.50, 0.57]
Subtotal (95% CI)			**39**			**40**	**14.2%**	**−0.03 [−0.47, 0.42]**
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%								
Test for overall effect: Z = 0.12 (P = 0.91)								
1.11.2 Healthy elderly								
Arnarson 2013	56.5	59.4	75	53.8	51.8	66	20.2%	0.05 [−0.28, 0.38]
Candow 2008	20	6	10	21	5	12	4.2%	−0.18 [−1.02, 0.67]
Holwerda 2018	102	4	21	105	4	19	6.8%	−0.74 [−1.38, −0.09]
Leenders 2013	110.12	26.75	27	111.53	22.83	26	9.3%	−0.06 [−0.59, 0.48]
Mori 2018	26.4	5.5	25	27.8	4.3	25	8.8%	−0.28 [−0.84, 0.28]
Nabuco 2018	59	12	21	56	13	23	7.9%	0.24 [−0.36, 0.83]
Stragier 2016	115.8	28	12	113.7	38.3	13	4.7%	0.06 [−0.72, 0.84]
Sugihara 2018	57.2	10.9	15	55.1	13.1	16	5.8%	0.17 [−0.54, 0.88]
Tieland 2012	76.8	17.3306	26	79.3	17.948	27	9.3%	−0.14 [−0.68, 0.40]
Trabal 2015	12.48	4.8153	7	6	4.6	4	1.6%	1.25 [−0.14, 2.64]
Verdijk 2009	115	5	13	111	5	13	4.5%	0.77 [−0.03, 1.58]
Villanueva 2014	363.2	131.4	7	327.7	87.3	7	2.7%	0.30 [−0.76, 1.35]
Subtotal (95% CI)			**259**			**251**	**85.8%**	**0.01 [−0.20, 0.22]**
Heterogeneity: Tau² = 0.03; Chi² = 14.36, df = 11 (P = 0.21); I² = 23%								
Test for overall effect: Z = 0.09 (P = 0.93)								
Total (95% CI)			**298**			**291**	**100.0%**	**−0.00 [−0.18, 0.18]**
Heterogeneity: Tau² = 0.01; Chi² = 14.53, df = 13 (P = 0.34); I² = 11%								
Test for overall effect: Z = 0.01 (P = 1.00)								
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%								

Figure 1: EEII Strength by Sarcopenia Condition



Study or Subgroup	PS + RT Mean	PS + RT SD	PS + RT Total	RT Mean	RT SD	RT Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.12.1 Sarcopenic elderly								
Nabuco 2019	44.8	8.6	13	42.8	7.1	13	21.2%	0.25 [−0.53, 1.02]
Subtotal (95% CI)			**13**			**13**	**21.2%**	**0.25 [−0.53, 1.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.62 (P = 0.53)								
1.12.2 Healthy elderly								
Candow 2008	19	4	10	9	4	12	15.5%	2.41 [1.26, 3.55]
Nabuco 2018	48	10	21	45	8	23	24.1%	0.33 [−0.27, 0.92]
Sugihara 2018	47	8.8	15	45.2	7.4	16	22.3%	0.22 [−0.49, 0.92]
Villanueva 2014	72.7	15	7	71.8	30.5	7	16.9%	0.04 [−1.01, 1.08]
Subtotal (95% CI)			**53**			**58**	**78.8%**	**0.67 [−0.18, 1.51]**
Heterogeneity: Tau² = 0.54; Chi² = 12.26, df = 3 (P = 0.007); I² = 76%								
Test for overall effect: Z = 1.55 (P = 0.12)								
Total (95% CI)			**66**			**71**	**100.0%**	**0.56 [−0.09, 1.21]**
Heterogeneity: Tau² = 0.36; Chi² = 12.58, df = 4 (P = 0.01); I² = 68%								
Test for overall effect: Z = 1.69 (P = 0.09)								
Test for subgroup differences: Chi² = 0.52, df = 1 (P = 0.47), I² = 0%								

Figure 2: EESS Strength by Sarcopenia Condition

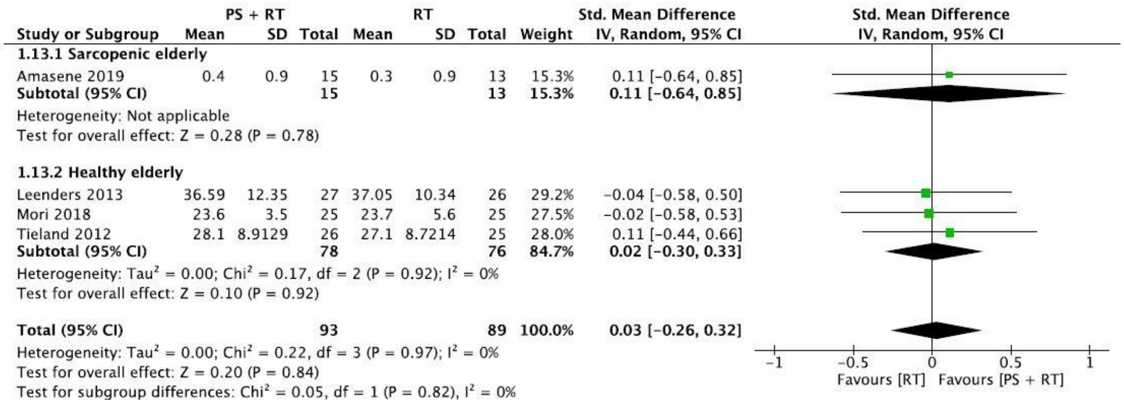


Figure 3: Handgrip by Sarcopenia Condition

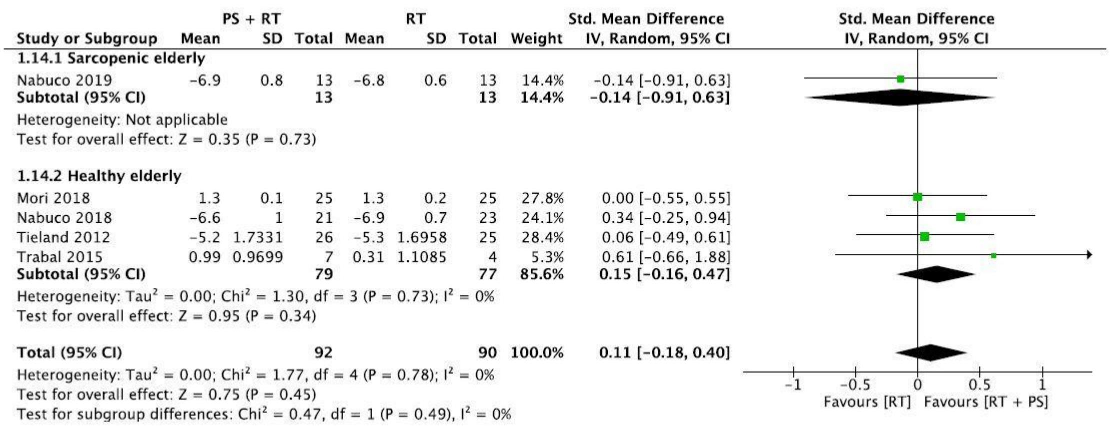


Figure 4: Gait Speed by Sarcopenia Condition

Study or Subgroup	PS + RT Mean	PS + RT SD	PS + RT Total	RT Mean	RT SD	RT Total	Weight	Mean Difference IV, Random, 95% CI
1.15.1 Sarcopenic elderly								
Amasene 2019	11.3	0.96	15	10.3	1.89	13	21.0%	1.00 [−0.14, 2.14]
Subtotal (95% CI)			**15**			**13**	**21.0%**	**1.00 [−0.14, 2.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.72 (P = 0.08)								
1.15.2 Healthy elderly								
Holwerda 2018	11.5	0.2	21	11.6	0.1	19	59.7%	−0.10 [−0.20, −0.00]
Tieland 2012	9.5	2.2282	26	9.2	2.1803	25	19.3%	0.30 [−0.91, 1.51]
Subtotal (95% CI)			**47**			**44**	**79.0%**	**−0.10 [−0.19, −0.00]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.42$, df = 1 (P = 0.52); $I^2 = 0\%$								
Test for overall effect: Z = 1.98 (P = 0.05)								
Total (95% CI)			**62**			**57**	**100.0%**	**0.21 [−0.44, 0.85]**
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 3.97$, df = 2 (P = 0.14); $I^2 = 50\%$								
Test for overall effect: Z = 0.63 (P = 0.53)								
Test for subgroup differences: $Chi^2 = 3.56$, df = 1 (P = 0.06), $I^2 = 71.9\%$								

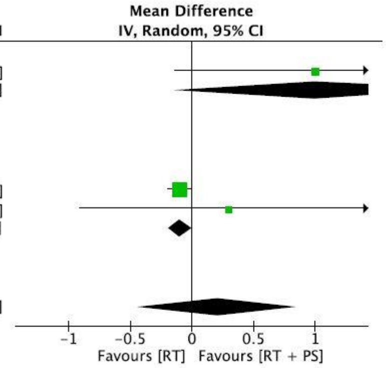


Figure 5: SPPB by Sarcopenia Condition

Study or Subgroup	PS + RT Mean	PS + RT SD	PS + RT Total	RT Mean	RT SD	RT Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.16.1 Sarcopenic elderly								
Amasene 2019	−10	2.81	15	−10.6	3.67	13	13.3%	0.18 [−0.56, 0.92]
Nabuco 2019	−10.7	1.4	13	−10.7	1.6	13	12.5%	0.00 [−0.77, 0.77]
Subtotal (95% CI)			**28**			**26**	**25.7%**	**0.09 [−0.44, 0.63]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.11$, df = 1 (P = 0.74); $I^2 = 0\%$								
Test for overall effect: Z = 0.34 (P = 0.73)								
1.16.2 Healthy elderly								
Leenders 2013	−6.15	1.32	26	−6.39	1.23	26	24.8%	0.19 [−0.36, 0.73]
Nabuco 2018	−10.5	1.7	21	−11	1.8	23	20.8%	0.28 [−0.31, 0.87]
Tieland 2012	−13.5	6.9323	26	−13.2	6.541	25	24.4%	−0.04 [−0.59, 0.51]
Trabal 2015	5.15	3.4987	7	1.92	2.5981	4	4.2%	0.92 [−0.40, 2.23]
Subtotal (95% CI)			**80**			**78**	**74.3%**	**0.18 [−0.14, 0.49]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.94$, df = 3 (P = 0.58); $I^2 = 0\%$								
Test for overall effect: Z = 1.11 (P = 0.27)								
Total (95% CI)			**108**			**104**	**100.0%**	**0.16 [−0.12, 0.43]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.12$, df = 5 (P = 0.83); $I^2 = 0\%$								
Test for overall effect: Z = 1.13 (P = 0.26)								
Test for subgroup differences: $Chi^2 = 0.07$, df = 1 (P = 0.79), $I^2 = 0\%$								

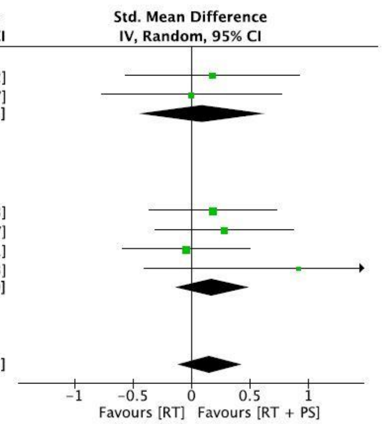


Figure 6: 5 Chair Raise by Sarcopenia Condition

Supplementary Appendix S5: Complete sensitivity Analysis evaluating heterogeneity across studies.

Lower Limb Strength

Study dropped out	SMD	95% CI	I^2
Arnason 2013	-0.01	[-0.22, 0.20]	17%
Candow 2008	0.01	[-0.18, 0.20]	16%
Holwerda 2018	0.05	[-0.12, 0.22]	0%
Leenders 2013	0.01	[-0.19, 0.20]	17%
Mori 2018	0.03	[-0.16, 0.21]	11%
Nabuco 2018	-0.02	[-0.21, 0.17]	13%
Nabuco 2019	0.01	[-0.18, 0.20]	17%
Stragier 2016	-0.00	[-0.19, 0.19]	17%
Sugihara 2018	-0.01	[-0.20, 0.18]	16%
Tieland 2012	0.02	[-0.18, 0.21]	16%
Trabal 2015	-0.02	[-0.18, 0.14]	0%
Verdijk 2009	-0.04	[-0.20, 0.13]	0%
Villanueva 2014	-0.01	[-0.19, 0.18]	16%

Zdzieblik 2015	-0.00	[-0.20, 0.19]	17%
None	-0.00	[-0.18, 0.18]	11%

SMD Standard Mean Difference; CI Confidence Interval; I^2 Heterogeneity Statistic

Upper Limb Strength

Study dropped out	SMD	95% CI	I^2
Candow 2008	0.24	[-0.12, 0.61]	0%
Nabuco 2018	0.66	[-0.25, 1.57]	76%
Nabuco 2019	0.67	[-0.18, 1.51]	76%
Sugihara 2018	0.68	[-0.18, 1,54]	75%
Villanueva 2014	0.68	[-0.09, 1.45]	75%
None	0.56	[-0.09, 1.21]	68%

SMD Standard Mean Difference; CI Confidence Interval; I^2 Heterogeneity Statistic

Handgrip

Study dropped out	SMD	95% CI	I^2
Amasene 2019	0.02	[-0.30, 0.33]	0%
Leenders 2013	0.06	[-0.29, 0.40]	0%
Mori 2018	0.05	[-0.29, 0.39]	0%
Tieland 2012	-0.00	[-0.34, 0.34]	0%
None	0.03	[-0.26, 0.32]	0%

SMD Standard Mean Difference; CI Confidence Interval; I^2 Heterogeneity Statistic

Gait Speed

Study dropped out	SMD	95% CI	I^2
Mori 2018	0.15	[-0.19, 0.50]	0%
Nabuco 2018	0.04	[-0.30, 0.37]	0%
Nabuco 2019	0.15	[-0.16, 0.47]	0%
Tieland 2012	0.13	[-0.21, 0.48]	0%
Trabal 2015	0.08	[-0.22, 0.38]	0%
None	0.11	[-0.18, 0.40]	0%

SMD Standard Mean Difference; CI Confidence Interval; I^2 Heterogeneity Statistic

SPPB

Study dropped out	SMD	95% CI	I^2
Amasene 2019	-0.10	[-0.19, -0.00]	0%
Holwerda 2018	0.67	[-0.16, 1.50]	0%
Tieland 2012	0.30	[-0.74, 1.33]	72%
None	0.21	[-0.44, 0.85]	50%

SMD Standard Mean Difference; CI Confidence Interval; I^2 Heterogeneity Statistic

5 Chair Raise

Study dropped out	SMD	95% CI	I^2
Amasene 2019	0.15	[-0.14, 0.44]	0%
Leenders 2013	0.15	[-0.17, 0.46]	0%
Nabuco 2018	0.12	[-0.18, 0.43]	0%

Nabuco 2019	0.18	[-0.11, 0.47]	0%
Tieland 2012	0.22	[-0.09, 0.53]	0%
Trabal 2015	0.12	[-0.15, 0.40]	0%
None	0.16	[-0.12, 0.43]	0%

SMD Standard Mean Difference; CI Confidence Interval; I^2 Heterogeneity Statistic

Artículo 5

Artículo 5	
Publicación	Effectiveness of Blood Flow Restriction Training on Muscle Strength and Physical Performance in Older Adults: A Systematic Review and Meta-analysis
Autores	Noé Labata-Lezaun, Luis Llurda-Almuzara, Vanessa González-Rueda, Carlos López-de-Celis, Simón Cedeño-Bermúdez, Joan Bañuelos-Pago, Albert Pérez-Bellmunt
Revista	Archives of Physical Medicine and Rehabilitation
Quartil (2022)	Q1
Cita	Labata-Lezaun N, Llurda-Almuzara L, González-Rueda V, López-de-Celis C, Cedeño-Bermúdez S, Bañuelos-Pago J, et al. Effectiveness of Blood Flow Restriction Training on Muscle Strength and Physical Performance in Older Adults: A Systematic Review and Meta-analysis. Arch Phys Med Rehabil. 2022 Sep;103(9):1848–57. doi: 10.1016/j.apmr.2021.12.015. PMID: 35026149
Enlace web	https://pubmed.ncbi.nlm.nih.gov/35026149/

Participación	Primer autor
Contribución del doctorando	Diseño del estudio, Realización de la revisión sistemática, Realización del meta-análisis, Redacción del artículo

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Archives of Physical Medicine and Rehabilitation 2022;000: 1−10

REVIEW ARTICLE

Effectiveness of Blood Flow Restriction Training on Muscle Strength and Physical Performance in Older Adults: A Systematic Review and Meta-analysis

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Abstract

Objective: To analyze the effectiveness of the blood flow restriction training in improving muscle strength and physical performance in older adults.

Data Sources: A systematic review and meta-analysis of randomized controlled trials was conducted. The Cochrane Library, PubMed, Web of Sciences, PEDro, Scopus, and ScienceDirect databases were systematically searched.

Study Selection: Articles were included if participants were 60 years or older and were considered healthy.

Data Extraction: The search strategy found a total of 363 studies. Finally, 10 articles were included in the systematic review, with a total of 278 healthy older adults analyzed.

Data Synthesis: The main results of the meta-analysis showed a statistical difference of muscle strength in favor of blood flow restriction training when compared with conventional training and no statistical differences when compared with high-intensity resistance training. Physical performance showed a nonstatistical difference between the blood flow restriction training, conventional training, and no training groups.

Conclusions: Blood flow restriction training is an interesting alternative to high-intensity strength training for improving muscle strength in older individuals who cannot perform high-load exercises.

Archives of Physical Medicine and Rehabilitation 2022;000:1−10

Blood Flow Restriction in Older Adults

Effectiveness of Blood Flow Restriction Training on Muscle Strength and Physical Performance in Older Adults: A Systematic Review and Meta-analysis

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ABSTRACT

Objective: To analyze the effectiveness of the blood flow restriction training in improving muscle strength and physical performance in older adults.

Design: A systematic review and meta-analysis of randomized control trials was conducted. The Cochrane Library, PubMed, Web of Sciences, PEDro, Scopus and ScienceDirect databases were systematically searched.

Participants: Articles were included if participants were 60 years or older and were considered as healthy.

Intervention: Blood flow restriction training compared with no training or high or load strength training.

Main Outcomes: Muscle strength and physical performance

Results: The search strategy found a total of 363 studies. Finally, ten articles were included in the systematic review, with a total of 278 healthy older adults analyzed. The main results of the meta-analysis showed a statistical difference of muscle strength in favor of blood flow restriction training when compared with conventional, and no statistical differences with high-intensity resistance training. Physical performance showed a non-statistical difference between the blood flow restriction training group and conventional training group and no training group.

Conclusion: Blood flow restriction training is an interesting alternative to high-intensity strength training for improving muscle strength in older people who cannot perform high-load exercises.

Keywords: Blood Flow Restriction, Resistance Training, Muscle Strength, Physical Functional Performance, Elderly

PROSPERO registration number: CRD42020186828

LIST OF ABBREVIATIONS

1RM: 1 repetition maximum

ACSM: American College of Sports Medicine

BFR: Blood flow restriction

BFRt: Blood flow restriction training

BFRw: Blood flow restriction walking

EWGSOP: European Working Group on Sarcopenia in Older People

HIRT: High-intensity resistance training

LIRT: Low-intensity resistance training

PEDro: Physiotherapy Evidence Database

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO: Prospective Register of Systematic Reviews

RPE: Rating of Perceived Effort

SPPB: Short Physical Performance Battery

Timed Up and Go test: TUG

INTRODUCTION

The notable increase in the older population that has occurred in recent decades represents a socioeconomic challenge in the coming years.(1) The current aging model, accompanied by a high rate of physical inactivity, causes a series of physical, psychological, and social changes that are ultimately related to higher mortality, morbidity, and dependence.(2) Specifically, at a physiological level, aging is mainly associated with a decrease in strength, muscle mass, and physical performance.(3) In fact, sarcopenia, traditionally defined as the age-related loss of muscle mass, has recently been reviewed by the European Working Group on Sarcopenia in Older People (EWGSOP). Loss of muscle strength has been prioritized as the major diagnostic criterion, being physical performance a measure of disease severity.(4)

Among all types of training, strength training has shown to be an effective strategy to mitigate or even reverse age-related physiological deconditioning.(5,6) Furthermore, high-intensity resistance training (70-85% 1 repetition maximum, (1RM)) has been found to produce greater improvements in terms of muscle strength and physical performance compared with lower intensities (55–65% 1RM).(7) In fact, a recent expert consensus on exercise in older adults recommends single and multi-joint training (such as bench press, squats, knee flexion and extension) with a frequency of 2-3 sessions per week, with an approximate volume of 1-3 sets of 8-12 repetitions per muscle group, and at an incremental intensity until reaching 70-80% 1RM, which would be considered high-intensity resistance training.(8)

However, introducing heavy loads in this type of population will not always be possible due to the overload of the joint tissues. This overload may cause musculoskeletal disorders, such us increase of osteoarthritis pain-related or increase the risk of injury. In these cases, the use of blood flow restriction (BFR) combined with low-intensity training could be an alternative to obtain similar benefits in terms of muscle strength to those of higher intensities but with lower mechanical stress.(9–12) Blood flow restriction consists of a partial restriction of arterial flow, combined with occlusion of venous flow, due to the application of a compression cuff placed proximally to the extremities.(13) It is usually combined with low-intensity resistance exercise, or with aerobic exercise.(14,15)

Although the mechanism of muscle hypertrophy and strength development through the blood flow restriction training (BFRt) remains unclear, there is a combination of factors that have been proposed to be responsible for these phenomena. These factors include the increased metabolic stress due to the tissue hypoxia, concentration metabolites, accumulation of reactive oxygen species, and cellular swelling that may induce an increase in the anabolic response. Other secondary factors include the activation of signaling pathways that lead to protein synthesis, the local and systemic synthesis of anabolic hormones, the increased recruitment of muscle fiber type II, and the stimulation of muscular satellite cells.(16–20)

At present, there are several studies that demonstrate the effectiveness of BFRt in young people and adults, in improving strength and muscle hypertrophy.(21–24) In fact, at the clinical level, these improvements may be of interest both in healthy people (21) and in rehabilitation processes after musculoskeletal pathologies, such as anterior cruciate ligament injuries (25,26) or knee osteoarthritis (27,28). Unfortunately, only few studies have focused on older adults yet. Specifically, a recent article by Centner et al. 2019 (29), meta-analyzed the effectiveness of BFRt in terms of muscle strength improvement in older adults. Based on the results of the 11 included studies, it was concluded that BFR was an effective strategy for increasing the effects of low intensity resistance training, but inferior in terms of strength gains compared with high intensity training. However, the inclusion criteria were individuals older than 50 years, and the search strategy was conducted in 2018. Furthermore, to date, there are no systematic reviews that analyze the effectiveness of the BFRt in improving the functional capacities of this age group. Based on the advances made in recent years in this field, a more specific review of the current literature is necessary. The purpose of this systematic review and meta-analysis is to analyze the effectiveness of the BFRt in improving muscle strength and physical performance in older adults.

METHODS

Protocol and Registration

The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist.(30) Registration in the International Prospective Register of Systematic Reviews (PROSPERO) was made before starting, with the code CRD42020186828.

Information Sources and Search

The PICO strategy was performed to develop an accurate search strategy. Population: adults older than 60 years (31–34); Intervention: blood flow restriction combined with any type of training; Comparison: other type of training methodologies or no training; Outcomes: muscle strength and physical performance. Randomized controlled trial filters proposed by the Cochrane Collaboration were added to the final search strategy.(35) The keywords included in the search are shown in Supplementary Appendix S1 (S1a) classified by the PICO strategy. PubMed, Web of Science, Scopus search engines, in addition to Cochrane Library, ScienceDirect and PEDro databases were used in the systematic review. Furthermore, a manual search was performed, and the bibliography from other similar systematic reviews was revised. The final search was performed on July 1th, 2021. Supplementary Appendix S2 shows the complete search strategy.

Outcomes

There were two main outcomes of the present systematic review and meta-analysis. At first, the assessment of the muscle strength capacity, focusing on those tests whose goal was to determine the ability to generate high forces against large resistances. Secondly, the assessment of physical performance, defined as an objectively measured whole body function related with mobility,(4) and including some other capacities such as agility, coordination, or speed.

Eligibility Criteria

The inclusion criteria were the following: 1) randomized controlled trial study design, 2) healthy participants, and 3) English language.

Exclusion criteria were the following: 1) hospitalized or post-surgery participants, 2) sample with cancer, diabetes, cardiovascular disease, or other several acute/chronic conditions.

Two researchers (S.C.B. and J.B.P.) independently screened the titles, abstracts, and full texts. A third reviewer (N.L.L.) decided in case of disagreement. Inter-rater agreement was evaluated by using Cohen's Kappa index.(36)

Data Extraction

For every included study, the following data was extracted: 1) author's last name, 2) year of publication, 3) sample size, 4) sample characteristics, 5) characteristics of the BFR (limb analyzed, type of BFR device, pressure, volume, intensity, duration, and frequency), 6) control group characteristics, 7) outcomes, and 8) main results.

Risk of Bias

In order to analyze the risk of bias of the randomized control trial studies included in the systematic review, as well as their methodological quality, Risk of Bias 2 tool (RoB 2)(37) and Physiotherapy Evidence Database (PEDro) scale (38) were respectively used. As they have shown a "moderate" agreement between them, they are considered not interchangeable.(39)

The Risk of Bias 2 tool (37) has been developed by the Cochrane Collaboration to evaluate an article in seven domains based on publication bias (sequence generation and allocation sequence concealment), performance bias (blinding participants and personnel), detection bias (blinding outcome assessor), attrition bias (incomplete data), reporting bias (selecting outcome reporting), and other bias (e.g. sample size). With these scores, it classifies each domain into “low risk”, “unclear risk”, or “high risk” of bias and gives a general view of the article methodology. The interrater reliability (IRR) of the tool has been shown as “slight” (IRR 0.16, 95% CI 0.08-0.24). (40)

The PEDro scale (38) is a scale designed by the Physiotherapy Evidence Database, composed of 11 items that asses the external validity (item 1), the internal validity (items 2-9), and the applicability or generalizability (items 10-11) of the study. Item 1 is not used to calculate the PEDro score. The interrater reliability (IRR) of the scale has been shown as “good” (IRR 0.68, 95% CI 0.57-0.76). (38)

Statistical Analyses

The Meta-analysis software used was RevMan Manager 5.3 (The Cochrane Collaboration, 2012). Every study, sample size, post-intervention means, and standard deviations (SD) were introduced in the software. If a SD was missing, it was calculated from the confidence interval (CI). In addition, when the studies did not report some of the required data, the corresponding author of the article was contacted to obtain them.

The outcomes of the studied variables (muscle strength and physical performance) were expressed as continuous across all the included articles. The articles which analyzed different comparison groups, such as no training and HIRT, were included in the meta-analysis individually as if they were different studies.

Due to the differences in the methodology of the studies, a random-effects model was chosen (DerSimonian-Laird approach(41)). Moreover, as different tools and procedures were used to measure the variables, the effect measure was reflected as the standard mean difference (SMD). Finally, the overall effect size was calculated with a 95% CI.

As proposed by Higgins et al.,(42) heterogeneity was classified as “small” (I2<25%), “moderate” (I2 25-75%), or “high” (I2>75%). In order to assess the individual influence of each study on the overall result, each study was removed once. Finally, the funnel plot visual interpretation was performed for all outcomes.

RESULTS

Search strategy

The search strategy found 363 studies (Cochrane Library: 87; PubMed: 43; Web of Science: 92; PEdro: 49; Scopus: 67; ScienceDirect: 25). Two additional studies were included after the manual search. A total of 166 studies were initially considered to be included after removing duplicates.

Study selection

In the preliminary filter, after the screening all of the titles and abstracts, 115 articles were excluded. Secondly, after assessing the full text, 42 articles were excluded. Ten studies met the inclusion criteria for the qualitative analysis after the full-text reading. Two studies dropped out from the meta-analysis for not presenting the required data after contacting the corresponding authors. Finally, 8 articles were included in the quantitative synthesis. Analysis of inter-observer agreement showed a Cohen’s Kappa index of k=0.75 categorized as “substantial” agreement.(36) The PRISMA flow chart is displayed in Figure 1

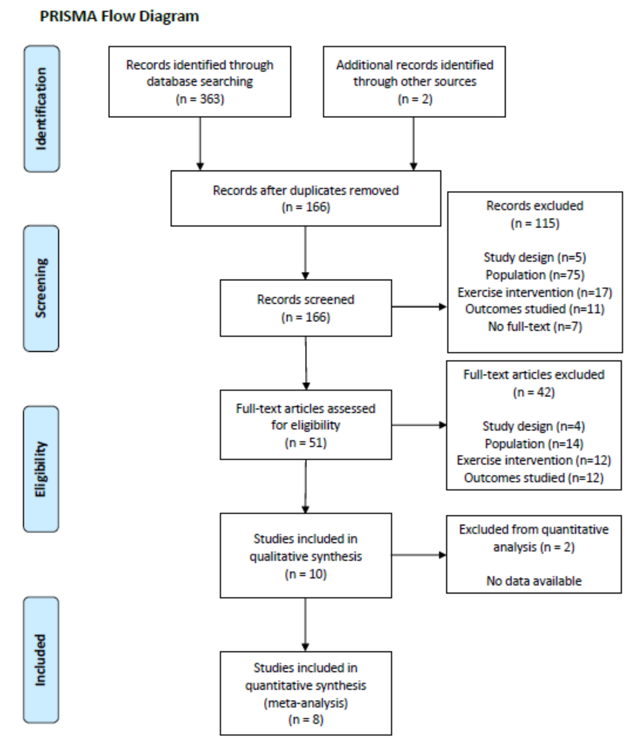

Figure 1. Flow Diagram

Study Characteristics

A total of 278 older adults were included in this systematic review. Regarding the gender of the sample, most of the studies included both male and female participants. Only two article studied only older women,(43,44) and another study did not report the gender of the sample (45). Sample sizes across studies ranged from 16 (46) to 56 subjects.(43)

Studies included in this systematic review involved participants from different countries. Four studies were conducted in Brazil (43–45,47) and Japan,(46,48,49) and one in USA,(50) Australia (51) and Denmark.(51)

In most studies, the training interventions had a duration of 12 weeks (n=6). Two studies had an intervention duration of 16 weeks,(43,44) one 8 weeks,(49) and one only 6 weeks.

(51) Nine of the ten studies included resistance training combined with BFR. One study included blood flow restriction combined with walking training (BFRw).(51) Training frequency varied from two to four days per week, with an intensity of 20-50% 1RM for the BFRt group. Five studies compared BFRt with a high-intensity resistance training (HIRT) of 70-80% 1RM, one study compared it with a dynamic balance training,(49) and three with a non-training control group. Moreover, seven of the nine studies used a pneumatic cuff and two used elastic cuffs.(46,48) Finally, nine articles analyzed outcomes related to muscle strength, and six to physical performance.

Table 1 summarizes the sample characteristics of the nine included articles.

Table 1: Characteristics of the studies included in the qualitative analysis.

	Population					BFRt Group					Control Group			
Study	**N (BFRt/CG/HIRT/LIRT)**	**Gender (M/F)**	**Age ± SD**	**Duration x Frequency**	**Exercises**	**Cuff type**	**Cuff width (cm)**	**Pressure (mm Hg)**	**Intensity**	**Sets x Reps**	**Type**	**Intensity**	**Sets x Reps**	**Outcomes**
Clarkson, 2017	19 (10/9/0/0)	M/F (11/8)	69.4	6 w 4 s/w	BFRw	Pneumatic	10.5	134 ± 4 (60% LOP)	4 km/h	10 min	WT	4 km/h	10 min	PP: TUG, 30″CST
Cook, 2017	36 (12/12/12/0)	M/F (NR)	75.6	12 w 2 s/w	LC LE	Pneumatic	6	184 ± 25 (x1.5 BSBP)	30-50% 1RM	3 x 15-30	NT HIRT	NA 70% 1RM	NA 3 x 10-15	ST: LE PP: SPPB

Galvao-Pereira, 2019	24(9/6/9/0)	F	63.1 ± 5.2	16 w 2 s/w	SQ	Pneumatic	18	85.8 ± 19.9 (50% LOP)	30% 1RM	4 x 15	NT HIRT	70% 1RM	3 x10	ST: SQ PP: TUG
Jørgensen, 2018	22 (11/11/0/0)	M/F (22/4)	69.0 ± 5.6	12 w 2 s/w	LP, LE, LC, CR, DF	Pneumatic	10	110	25RM	3-4 x 25	NT	NA	NA	ST: LE PP: TUG
Letieri, 2018	45 (11/12/10/12)	F	68.8 ± 5.09	16 w 3 s/w	SQ, LP LE, LC	Pneumatic	NR	105.45 ± 6.5 (80% LOP)	20-30% 1RM	3-4 x 15-30	NT HIRT LIRT	NA 70-80% 1RM NR	NA 3-4 x 6-8 NR	ST: LE
Libardi, 2015	23 (9/6/8/0)	NR	64.7 ± 4.1	12 w 4 s/w	LP	Pneumatic	17.5	67 ± 8.0 (50% LOP)	20-30% 1RM	4 x 15-30	NT HIRT	NA 70-80% 1RM	NA 4 x 10	ST: LP
Vechin, 2015	23 (8/7/8/0)	M/F (14/9)	64.04 ± 3.81	12 w 2 s/w	LP	Pneumatic	18	71 ± 9 (50% LOP)	20-30% 1RM	4 x 15-30	NT HIRT	NA 70-80% 1RM	NA 4 x 10	ST: LP
Yasuda,	19 (9/10/0/0)	M/F (5/14)	69.4	12 w 2 s/w	LP LE	Elastic	NR	120-270	20-30%	NR	NT	NA	NA	ST: LE

2014									1RM					
Yasuda, 2013	16 (8/8/0/0)	M/F (5/11)	68.0	12 w 2 s/w	LP LE	Elastic	5	120-270	20-30% 1RM	4 x 15-30	NT	NA	NA	ST: LE PP: 30″CST
Yokokawa, 2008	51 (24/27/0/0)	M/F (17/34)	72.0	8 w 2 s/w	LLME	Pneumatic	3.3	70-150 (x1.2 BSBP)	NR	NR	DBT	NA	NA	ST: LE PP: TUG

M: male; F: Female; SD: standard deviation; w: week; s/w: sessions per week; BFRt: blood flow restriction training; BFRw: blood flow restriction walking; WT: walking training; LC: leg curl; LOP: limb occlusion pressure; BSBP: brachial systolic blood pressure; LE: leg extension; LP: leg press; CR: calf rise; DF: ankle dorsiflexion; SQ: squat; LLME; Lower limb multi-exercises; SPPB: short physical performance battery; TUG: timed up and go test; 30’’CST: 30-seconds chair stand test; NT: no training; HIRT: high-intensity resistance training; LIRT: low-intensity resistance training; DBT: dynamic balance training; ST: muscle strength; PP: physical performance; RM: repetition maximum; NA: not applicable; NR: no reported.

Risk of Bias Assessment

The average PEDro scale score was 5.5 points out of 10, which can be interpreted as a “fair” methodological quality across the included studies (Supplementary Appendix S1cb).(52)

Figure 2 shows the RoB 2 tool summary and graph. Nine studies had at least one domain with an “unclear risk”, and four studies had one domain as a “high risk”. Seven of the studies had issues with the allocation procedure. Nine studies had issues with the participants and personnel blinding, and seven with the assessor blinding.

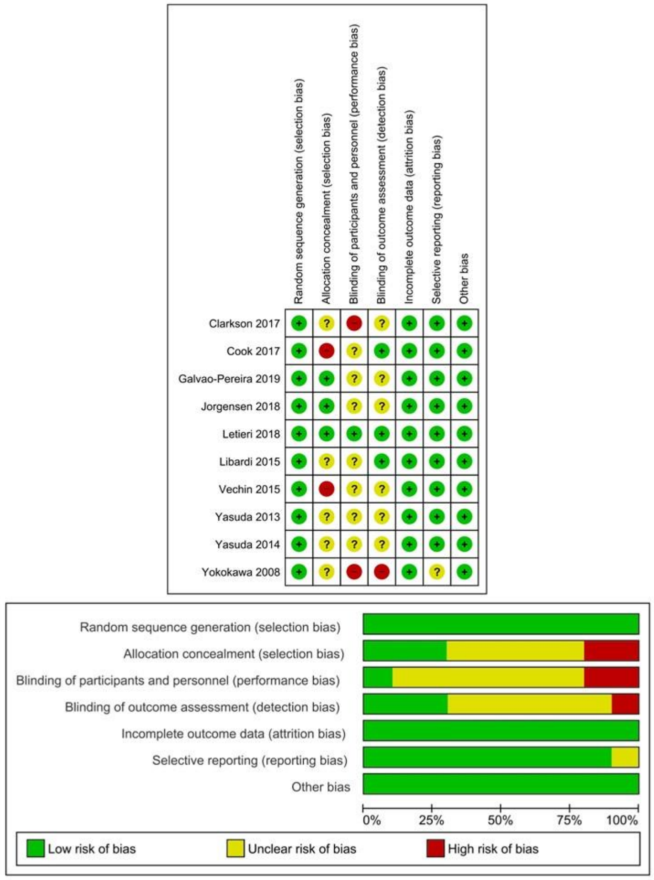

Figure 2. Risk of bias summary v2

Muscle Strength

The primary outcome assessed was muscle strength. It was assessed using the one-repetition maximum (1RM) method during a leg extension exercise for the lower extremity. This was the common procedure throughout the studies except in the studies conducted by Vechin et al.(47) and Libardi et al.,(45) where leg press strength was chosen; in the study of Yokokawa et al.,(49) where a leg extension dynamometry was used; and in Galvao-Pereira et al.,(44) where a free bar squat was used. Moreover, in the studies of Letieri et al.(43) and Yokokawa et al.(49) both limbs were studied separately, so authors decided to analyze only the right limb. Furthermore, regarding the meta-analysis, Cook et al.,(50) Libardi et al.(45) and Vechin et al.(47) compared the BFR training not only with a non-training control group, but with a high-intensity resistance training (HIRT) group. Letieri et al.(43) included a third comparison group of low-intensity resistance training (LIRT) group. Numerical data from Galvao-Pereira et al. (44) was not available and could not be included in the meta-analysis.

The global comparison of BFRt against other interventions (non-training, HIRT and LIRT) (Figure 3) included a total sample size of 279, 138 for the BFRt group and 141 for the "other interventions group". The overall SMD was 0.47 with a 95% confidence interval of [0.02, 0.93] and an overall effect of Z = 2.04 (P < .04). The heterogeneity showed by I2 statistic was moderate (I2 = 69%). In order to investigate this heterogeneity, all studies were removed once from the analysis. When the Letieri et al.(43) study was removed, the heterogeneity was 0%. Visual interpretation of the funnel plot reveals no evidence of publication bias for this outcome.

	BFRt			Other interventions				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Cook 2017	43.5833	19.57887	12	38.6742	20.89333	12	8.4%	0.23 [-0.57, 1.04]
Cook 2017 (2)	43.5833	19.57887	12	58.9697	24.70205	12	8.3%	-0.67 [-1.49, 0.16]
Jorgensen 2018	0.62	0.55	11	0.53	0.5	11	8.2%	0.16 [-0.67, 1.00]
Letieri 2018	119.47	14.4	11	80.07	10.96	12	6.1%	2.99 [1.73, 4.24]
Letieri 2018 (2)	119.47	14.4	11	116.01	14.5	10	8.1%	0.23 [-0.63, 1.09]
Letieri 2018 (3)	119.47	14.4	11	85.88	15.03	12	7.0%	2.20 [1.12, 3.27]
Libardi 2015	200.33	73.932	9	202.53	84.187	6	7.2%	-0.03 [-1.06, 1.01]
Libardi 2015 (2)	200.33	73.932	9	231.625	81.475	8	7.5%	-0.38 [-1.35, 0.58]
Vechin 2015	316	141	8	203	84	7	6.9%	0.90 [-0.18, 1.98]
Vechin 2015 (2)	316	141	8	266	140	8	7.4%	0.34 [-0.65, 1.33]
Yasuda 2013	64	26	9	55	27	10	7.8%	0.32 [-0.58, 1.23]
Yasuda 2014	66	27	8	63	24	8	7.5%	0.11 [-0.87, 1.09]
Yokokawa 2008	24.7	8.1	19	20.9	6.1	25	9.5%	0.53 [-0.08, 1.14]
Total (95% CI)			**138**			**141**	**100.0%**	**0.47 [0.02, 0.93]**

Heterogeneity: Tau² = 0.47; Chi² = 38.71, df = 12 (P = 0.0001); I² = 69%
Test for overall effect: Z = 2.04 (P = 0.04)

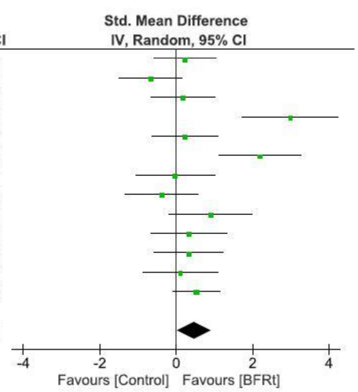

Figure 3. Effectiveness of BFRt against "other interventions" on muscle strength.

Supplementary Appendix S3 (S3a) shows the comparison BFRt against the non-training group separately. A hundred and twenty people (59 for the BFRt group and 61 for the non-training group) were included. Analysis shows an overall SMD of 0.70 with a 95% confidence interval of [-0.02, 1.43] and an overall effect of Z = 1.90 (P < .06). The heterogeneity showed by I2 statistic was moderate (I2 = 71%). When Letieri et al.(43) study was removed, the heterogeneity was 0%. Visual interpretation of the funnel plot reveals no evidence of publication bias for this outcome.

Supplementary Appendix S3 (S3b) shows the comparison BFRt against HIRT, including a total sample of 78 (40 for the BFRt group and 38 for the HIRT group). Analysis shows an overall SMD of -0.15 with a 95% confidence interval of [-0.63, 0.34] and an overall effect of Z = 0.59 (P < .55). The heterogeneity showed by I2 statistic was low (I2 = 12%), and the visual interpretation of the funnel plot revealed no evidence of publication bias for this outcome.

Physical Performance

The secondary outcome assessed in the studies was physical performance. When more than one test was used in the study, authors chose the more functional one according to their expert judgment. Six studies assessed the physical performance using the Short Physical Performance Battery (SPPB),(50) the Timed Up and Go test (TUG),(44,49,51) and the 30-seconds Chair Stand test (30"CST).(48) Three studies compared the BFRt with a non-training control group and one with a dynamic balance training.(49) Moreover, Cook et al.(50) included a second comparison group of high-intensity resistance training (HIRT) group. Finally, Clarkson et al. (51) compared BFR combined with walking training, with walking training alone. Numerical data from Galvao-Pereira et al. (44) and Clarkson et al. (51) were not available and could not be included in the meta-analysis.

When comparing BFRt with other interventions (including non-training and HIRT group), a total of 63 participants were included in the intervention group and 70 participants were included in the control group. Meta-analysis (Figure 4) shows an overall SMD of 0.38 with a 95% confidence interval of [-0.05, 0.81] and an overall effect of Z = 1.72 (P < .20). The heterogeneity showed by I2 statistic was low (I2 = 33%). When the Yokokawa et al.(49) study was removed, the heterogeneity was 0%. Visual interpretation of the funnel plot reveals no evidence of publication bias for this outcome.

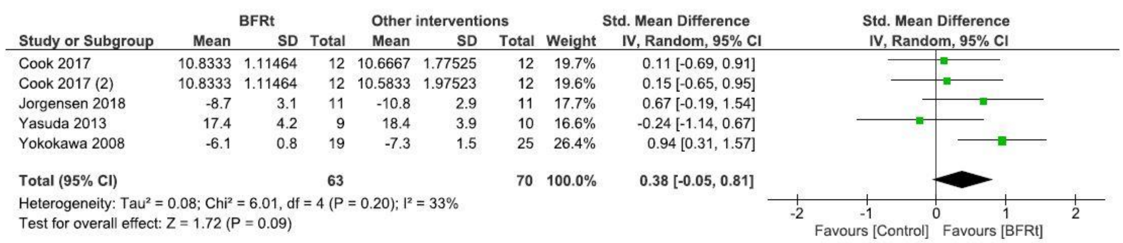

Figure 4. Effectiveness of BFRt against "other interventions" on physical performance.

Comparison of BFRt with non-training groups only (Supplementary Appendix S3c) included a total sample of 32 participants for the BFRt groups and 33 for the non-training group. The overall SMD was 0.19 with a 95% confidence interval of [-0.31, 0.69] and overall effect of Z = 0.74 (P < .46). The heterogeneity showed by I2 statistic was low (I2 = 4%) and the visual interpretation of the funnel plot revealed no evidence of publication bias for this outcome.

The complete sensitivity analysis and funnel plots are also available in the Supplementary Appendix S4 and S5.

DISCUSSION

The present article aims to summarize the effects of the BFRt on the muscle strength and physical performance in the healthy older adult population. This systematic review summarizes findings from a total of 278 participants included in ten studies. Although, similar previous studies did exist, they did not focus exclusively on the older adults.(23,24) These studies included populations under 60 years,(29,53,54) they analyzed different types of studies other than randomized control trials.(53,54)

Muscle Strength

The findings in our meta-analysis suggest that BFRt is significantly more effective than conventional interventions in improving muscle strength. These results coincide with the study by Maciel-Batista et al.,(54) carried out on people over 50. However, when compared to a non-training control group, the improvements in muscle strength are surprisingly not statistically significant. This difference could be due to the fact that the number of samples included in this comparison is considerably reduced.

One of the main results of this meta-analysis is that the comparison between BFRt and HIRT shows differences between the two types of training and favors HIRT. However, these differences are not statistically significant. These results support the idea that BFRt could be an alternative to resistance training, as HIRT does not provide any additional benefits in terms of muscle strength.(22) The current evidence on the importance of high-intensity strength training in improving health is unquestionable. (8) In fact, the American College of Sports Medicine (ACSM) recommends training at intensities between 60-

80%1RM to maximize strength gains in older adults. (55) However, in clinical practice, for untrained older adults, it can be difficult to work at these intensities. In this sense, the application of BFRt could be interesting to minimize mechanical loads on tissues. This could be useful in the early phases of training after injury, hospitalization or after a long period of physical inactivity, where high loads might not be tolerated by the patient.(56,57) In addition, in novice individuals, introducing BFR combined with light loads could be used during the initial conditioning period and improvement of movement technique, by decreasing the subjective perception of threat posed by training with high loads.

Comparing these results with previous meta-analyses, Hughes et al.(58) and Lixandrão et al.(21) found significant differences in favor of HIRT in the general population. In addition, the study by Centner et al.(29) in the population over 50 years old also found significant differences in favor of HIRT. In view of our results, it could be suggested that, in older adults, the BFRt alternative could be more beneficial when needed.

It is important to highlight the heterogeneity of the studies. Specifically, in the study of Letieri et al.,(43) the comparisons between BFRt with no training and LIRT are highly favorable towards the BFRt compared to other studies. However, when analyzing its methodological quality, we find that it is above the average of the studies, therefore, we should trust these results. It should be taken into account that this study was the one with the longest duration (16 weeks). Thus, we could suspect that if the rest of the interventions had been prolonged in time, the results would have been more in favor of the BFRt when compared to the non-training group.

Physical Performance

The results of this meta-analysis show that BFRt does not produce statistically significant improvements in physical performance compared to other treatments. These results are consistent with those obtained by Maciel-Batista et al.(54) in people over 50. On the other hand, a systematic review by Baker et al.(53) observed improvements in physical performance in this same population, as well as Bennett et al.(23) did in a general population. It is important to emphasize that the number of studies included in our meta-analysis is only four articles with a total sample of 133 volunteers, so the results may not be generalizable.

Interestingly, the studies that produce the greatest improvements in physical performance are those of Jørgensen et al.(51) and Yokokawa et al.(49) In these two studies, the number of exercises used in the training protocol was higher compared to the rest of the studies, which only included 1-2 exercises. It would make sense to think that it is necessary to include a certain variety of exercises to achieve an improvement in physical performance, since this does not depend solely on a single pattern of movement or muscle group.(7)

Nevertheless, it is important to note that pooling different measures of physical performance assessment in the same meta-analysis may lead to a cautious interpretation of the results. This could be mainly due to the limited number of studies assessing the physical performance. On the other hand, it might be due to the lack of a single test for the assessment of physical performance.

Finally, although it could not be pooled in the meta-analysis, the study by Clarkson et al.(51) shows significant improvements in the group that combined BFRw compared with walking training alone. In that case, as the authors of the study themselves recognize, although the walking protocol was the same for both groups, the internal load, measured by the rating of perceived effort (RPE), was greater in the BFRw group. It would be interesting to analyze whether these significant improvements in physical performance would have occurred at the same RPE, for example, by increasing the walking speed in the control group. However, in older people where performance issues make it impossible to increase walking speed, BFRw could be a suitable alternative, if the internal load is well tolerated. In this sense, as this was only a clinical trial in a small sample, the results should be extrapolated with caution.

Adverse effects

Referring to adverse effects, five studies reported no problems following BFR application. The remaining three studies did not mention any possible adverse effects. These results are consistent with the review by Minniti et al. 2019 (59) in people with musculoskeletal disorders, in which they concluded that BFRt is a safe approach to strength improvement, with the same injury rate as conventional strength training. Considerations on BFR application methodology and safety have been well covered in the recent article by Patterson et al. 2019. (13)

Limitations

Regarding the limitations, we could highlight the heterogeneity of the training protocols among the different studies. These differences would mainly refer to the duration of the intervention, as well as the characteristics of the training of the control group (mainly the types of training, volume, intensity, and frequency). In addition, with respect to the BFRt protocol, it is worth noting the difference between the cuff pressures, as well as the type and width of the cuff.

Furthermore, it is important to note the differences between the interventions within the same study, in most cases the volume loads are not equal, but rather two different training protocols are compared. In this way, it would be possible that the differences in muscle strength or physical performance in each of the studies were due to a difference in volume load.

In addition, despite having ensured a good randomization of the groups in all the included studies, the baseline values of the variables studied slightly varied in some cases between the intervention and the control group. The difference between both groups could have varied when taking as a reference the values of the post-training for the meta-analysis.

The results of the quality analysis should be taken with caution, especially those referring to ROB 2. Although ROB 2 is the tool recommended by the Cochrane Collaboration to assess the risk of bias, its inter-rater reliability is considered low (40). Moreover, the results obtained with the PEDro scale are considered "fair". More studies with good methodological quality are needed to corroborate the results obtained from this meta-analysis.

Finally, although the vast majority of the scientific literature is written in English, only including only articles in English may have limited the inclusion of articles in other languages.

CONCLUSION

In view of the present results, it can be said that BFRt is an interesting alternative to high-intensity strength training for improving muscle strength in older people who cannot perform high-load exercises. Current literature does not support BFRt in isolated exercises in order to improve physical performance. However, quality and longer-term studies are needed to confirm the results.

HIGHLIGHTS

- Although blood flow restriction training (BFRt) has been used during the las decade, there is still little evidence of its use in older adults.
- No significant differences have been found between high-intensity resistance training (HIRT) and BFRt with respect to muscle strength improvement. More studies are needed to analyze the effectiveness of BFRt in the improvement of physical performance.
- BFRt may be a good alternative to HIRT in older adults for improving muscle strength when this type of training cannot be performed.

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Figure Legend

Figure 1. Search PRISMA flow diagram.

Figure 2. Risk of bias summary.

Figure 3. Effectiveness of BFRt against “other interventions” on muscle strength.

Figure 4. Effectiveness of BFRt against “other interventions” on physical performance.

Supplementary Appendix S1: Tables

Table S1a: Keywords used for the search strategy.

Population	Intervention	Outcomes
Aged	BFR training	Physical fitness
Old people	Blood flow restriction	Physical function
Elderly	Blood flow restricted	Functionality
Aging	Tourniquet training	Functional capacity
Older people	Kaatsu	Functional ability
Older adults	Occlusion training	Functional parameters
Old adults		Functional capabilities
Frail		Performance
Senior		Fitness
Geriatric		Strength
		Resistance
		Endurance
		Balance
		Stability
		Agility

Mobility
Gait
Speed
Locomotion
Fall
Falling
Handgrip
SPPB
Tandem
TUG
Quality of life

Table S1b: PEDro scale.

Study	1	2	3	4	5	6	7	8	9	10	11	Total
Clarkson, 2017	1	1	0	1	0	0	0	1	0	1	1	5
Cook, 2017	1	1	0	1	0	0	1	1	1	1	1	7
Galvao-Pereira, 2019	1	1	1	1	0	0	0	1	1	1	1	7
Jørgensen, 2018	1	1	0	0	0	0	0	1	1	1	1	5
Letieri, 2018	1	1	1	1	1	1	0	0	0	1	1	7
Libardi, 2015	1	1	0	0	0	0	0	1	1	1	1	5
Vechin, 2015	1	1	0	1	0	0	0	0	0	1	1	4
Yasuda, 2013	1	1	0	1	0	0	0	0	1	1	1	5
Yasuda, 2014	1	1	0	0	0	0	0	0	1	1	1	4
Yokokawa, 2008	1	1	0	1	0	0	0	1	1	1	1	6
Average												**5.5***

1: Inclusion/Exclusion Criteria; 2: Random Allocation of Participants; 3: Concealed Allocation; 4: Similarity Between Groups at Baseline; 5: Participant Blinding; 6: Therapist Blinding; 7: Assessor Blinding; 8: Fewer than 15% Dropouts; 9: Intention- to-Treat Analysis; 10: Between- Group Statistical Comparisons; 11: Point

Measures and Variability Data. * Item 1 is not used to calculate the PEDro score.

Supplementary Appendix S2: Complete literature search

PubMed Search Formula

#1 (aged [mh] OR aged OR "old people" OR "older people" OR "older adults" OR "old adults" OR elderly OR senior OR geriatric OR frail)

#2 ("bfr training" OR "blood flow restriction" OR "blood flow restricted" OR "tourniquet training" OR kaatsu OR "occlusion training")

#3 (physical fitness [mh] OR physical fitness OR functionality OR Performance OR Strength OR Resistance OR Endurance OR balance OR stability OR agility OR mobility OR Gait OR Speed OR Locomotion OR fall OR Handgrip OR SPPB OR Tandem OR TUG OR "Timed up and go")

#4 (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [TiAb]) OR placebo [TiAb] OR clinical trials as topic [mesh: noexp] OR randomly [TiAb]) OR trial [Ti]) NOT (animals [mh] NOT humans [mh])

#6 #1 AND #2 AND #3 AND #4

Results: 43

Date: 01/07/2021

Cochrane Library Search Formula

#1 MeSH descriptor: [Aged] explode all trees

#2 (aged):ti,ab,kw

#3 ("old people"):ti,ab,kw

#4 ("old adults"):ti,ab,kw

#5 ("older people"):ti,ab,kw

#6 ("older adults"):ti,ab,kw

#7 (ageing):ti,ab,kw

#8 (frail):ti,ab,kw

#9 (elderly):ti,ab,kw

#10 (senior):ti,ab,kw

#11 (geriatric):ti,ab,kw

#12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

#13 MeSH descriptor: [Physical Fitness] explode all trees

#14 ("physical function"):ti,ab,kw

#15 (functionality):ti,ab,kw

#16 ("functional capacity"):ti,ab,kw

#17 ("functional ability"):ti,ab,kw

#18 ("functional parameters"):ti,ab,kw

#19 ("functional capabilities"):ti,ab,kw

#20 (performance):ti,ab,kw

#21 (strength):ti,ab,kw

#22 (endurance):ti,ab,kw

#23 (balance):ti,ab,kw

#24 (resistance):ti,ab,kw

#25 (stability):ti,ab,kw

#26 (agility):ti,ab,kw

#27 (mobility):ti,ab,kw

#28 (speed):ti,ab,kw

#29 (gait):ti,ab,kw

#30 (locomotion):ti,ab,kw

#31 (falls):ti,ab,kw

#32 (falling):ti,ab,kw

#33 (handgrip):ti,ab,kw

#34 (SPPB):ti,ab,kw

#35 (Tandem):ti,ab,kw

#36 (TUG):ti,ab,kw

#37 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36

#38 (“BFR training”):ti,ab,kw

#39 (“blood flow restriction”):ti,ab,kw

#40 (“blood flow restricted”):ti,ab,kw

#41 (“tourniquet training”):ti,ab,kw

#42 (kaatsu):ti,ab,kw

#43 (“occlusion training”):ti,ab,kw

#44 #38 #39 OR #40 OR #41 OR #42 OR #43

#45 #12 AND #38 AND #44

Results: 87

Date: 01/07/2021

Web of Science Search Formula

#1 ALL=(aged OR “old people” OR “older people” OR “older adults” OR “old adults” OR elderly OR senior OR geriatric OR frail)

#2 ALL=("bfr training" OR "blood flow restriction" OR "blood flow restricted" OR "tourniquet training" OR kaatsu OR "occlusion training")

#3 ALL=(physical fitness OR functionality OR Performance OR Strength OR Resistance OR Endurance OR balance OR stability OR agility OR mobility OR Gait OR Speed OR Locomotion OR fall OR Handgrip OR SPPB OR Tandem OR TUG OR "Timed up and go")

#4 TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*)

#6 (TS=#1 AND #2 AND #3 AND #4)

Results: 92

Date: 01/07/2021

PEDro

“blood flow restriction”

Results: 49

Date: 03/10/2021

Scopus

(TITLE-ABS-KEY (aged OR "old people" OR "older people" OR "older adults" OR "old adults" OR elderly OR senior OR geriatric OR frail) AND TITLE-ABS-KEY ("bfr training" OR "blood flow restriction" OR "blood flow restricted" OR "tourniquet training" OR kaatsu OR "occlusion training") AND TITLE-ABS-

KEY (physical AND fitness OR physical AND fitness OR functionality OR performance OR strength OR resistance OR endurance OR balance OR stability OR agility OR mobility OR gait OR speed OR locomotion OR fall OR handgrip OR sppb OR tandem OR tug OR "Timed up and go"))

Results: 67

Date: 03/10/2021

ScienceDirect

Title, abstract, keywords: (aged OR “older adults” OR elderly) AND ("bfr training" OR "blood flow restriction" OR kaatsu OR "occlusion training")

Results: 25

Date: 03/10/2021

Supplementary Appendix S3: Forest Plots

Study or Subgroup	BFRt Mean	BFRt SD	BFRt Total	No training Mean	No training SD	No training Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cook 2017	43.5833	19.57887	12	38.6742	20.89333	12	18.4%	0.23 [-0.57, 1.04]
Jorgensen 2018	0.62	0.55	11	0.53	0.5	11	18.1%	0.16 [-0.67, 1.00]
Letieri 2018	119.47	14.4	11	80.07	10.96	12	14.0%	2.99 [1.73, 4.24]
Vechin 2015	316	141	8	203	84	7	15.6%	0.90 [-0.18, 1.98]
Yasuda 2013	64	26	9	55	27	10	17.3%	0.32 [-0.58, 1.23]
Yasuda 2014	66	27	8	63	24	8	16.6%	0.11 [-0.87, 1.09]
Total (95% CI)			**59**			**60**	**100.0%**	**0.70 [-0.02, 1.43]**

Heterogeneity: Tau² = 0.58; Chi² = 17.36, df = 5 (P = 0.004); I² = 71%
Test for overall effect: Z = 1.89 (P = 0.06)

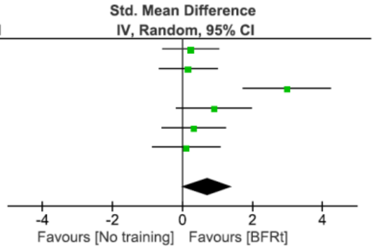

Figure S3a. Effectiveness of BFRt against no training on muscle strength.

Study or Subgroup	BFRt Mean	BFRt SD	BFRt Total	HIRT Mean	HIRT SD	HIRT Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cook 2017	43.5833	19.57887	12	58.9697	24.70205	12	29.2%	-0.67 [-1.49, 0.16]
Letieri 2018	119.47	14.4	11	116.01	14.5	10	27.3%	0.23 [-0.63, 1.09]
Libardi 2015	200.33	73.932	9	231.625	81.475	8	22.3%	-0.38 [-1.35, 0.58]
Vechin 2015	316	141	8	266	140	8	21.3%	0.34 [-0.65, 1.33]
Total (95% CI)			**40**			**38**	**100.0%**	**-0.15 [-0.63, 0.34]**

Heterogeneity: Tau² = 0.03; Chi² = 3.40, df = 3 (P = 0.33); I² = 12%
Test for overall effect: Z = 0.59 (P = 0.55)

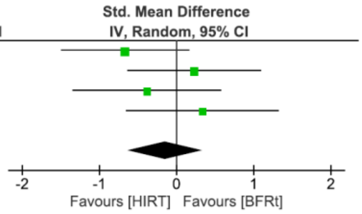

Figure S3b. Effectiveness of BFRt against HIRT on muscle strength.

Study or Subgroup	BFRt Mean	BFRt SD	BFRt Total	No training Mean	No training SD	No training Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cook 2017	10.8333	1.11464	12	10.6667	1.77525	12	37.6%	0.11 [-0.69, 0.91]
Jorgensen 2018	-8.7	3.1	11	-10.8	2.9	11	32.6%	0.67 [-0.19, 1.54]
Yasuda 2013	17.4	4.2	9	18.4	3.9	10	29.8%	-0.24 [-1.14, 0.67]
Total (95% CI)			**32**			**33**	**100.0%**	**0.19 [-0.31, 0.69]**

Heterogeneity: Tau² = 0.01; Chi² = 2.09, df = 2 (P = 0.35); I² = 4%
Test for overall effect: Z = 0.74 (P = 0.46)

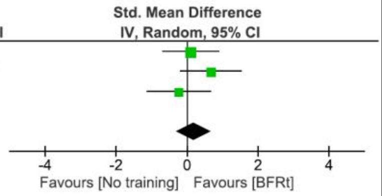

Figure S3c. Effectiveness of BFRt against no training on physical performance.

Artículo 6

Artículo 6	
Publicación	Effectiveness of multicomponent training on physical performance in older adults: A systematic review and meta-analysis
Autores	Noé Labata-Lezaun, Vanessa González-Rueda, Luis Llurda-Almuzara, Carlos López-de-Celis, Jacobo Rodríguez-Sanz, Joan Bosch, Germán Vicente-Rodríguez, Dorota Gorczakowska, Paola Araluze-Arizti, Albert Pérez-Bellmunt
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Contribución del doctorando	Diseño del estudio, Realización de la revisión sistemática, Realización del meta-análisis, Redacción del artículo

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Review

Effectiveness of multicomponent training on physical performance in older adults: A systematic review and meta-analysis

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ABSTRACT

Multicomponent training (MCT) is characterized by the combination of at least 3 types of training. The purpose of this meta-analysis was to assess the effectiveness of MCT programs for improving physical performance in healthy older adults.

A systematic review and meta-analysis of randomized control trials (RCTs) was conducted. The systematic search was performed in the Web of Sciences, PubMed (MEDLINE), and Cochrane Library databases.

Articles were included if participants were healthy and 65 years or older, and the control group did not perform any type of training. Studies were excluded if the interventions lasted less than 8 weeks. PEDro scale and Risk of Bias tool (RoB) were used in order to assess the quality of the articles.

The search strategy found a total of 388 studies. After inclusion and exclusion criteria, 19 studies were included for the qualitative analysis. Finally, 13 articles were included in the meta-analysis, with a total of 808 healthy older adults analyzed.

The main results of the meta-analysis showed that MCT improves physical performance significantly more than no training (SMD: 0.78; 95% CI: 0.55, 1.00; $Z = 6.84$, $p < 0.01$; $I^2 = 54\%$). In addition, the MCT also seems to significantly increase in upper and lower limb strength, walking speed and aerobic capacity.

MCT improves general functionality, strength in upper and lower extremities, walking speed and aerobic capacity. Implementation of MCT programs should be encouraged as an effective strategy in the prevention of adverse conditions in the older adult.

Effectiveness of multicomponent training on physical performance in older adults: A systematic review and meta-analysis

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The main results of the meta-analysis showed that MCT improves physical performance significantly more than no training (SMD: 0.78; 95% CI: 0.55, 1.00; Z=6.84, $p<0.01$; $I^2=54\%$). In addition, the MCT also seems to significantly increase in upper and lower limb strength, walking speed and aerobic capacity.

MCT improves general functionality, strength in upper and lower extremities, walking speed and aerobic capacity. Implementation of MCT programs should be encouraged as an effective strategy in the prevention of adverse conditions in the older adult.

KEYWORDS

Exercise, Physical Functional Performance, Muscle Strength, Aged

PROSPERO registration number: CRD42020186796

INTRODUCTION

Currently, 20% of the total European population is over 65 years, and these numbers are still increasing (Tornero-Quiñones, Sáez-Padilla, Díaz, Robles, & Robles, 2020). Moreover, it is estimated that about 17% of this older adults could be in a state of fragility (Wleklik et al., 2020). The predominance of a pro-inflammatory state typical of aging is related to structural, (Beaudart et al., 2019) metabolic changes (Bosco et al., 2021) and neuroendocrine changes (Pedersen, 2013) that influence the musculoskeletal system, and ultimately lead to a decrease in physical performance (Beaudart et al., 2019). These changes must be understood in a multidirectional way with the rest of the systems in such a way that this "inflammageing" could provoke, for example, changes in the muscular tissue, alterations in the microbiota, or psychological disorders, and in turn all these states could influence each other generating a feedback (Ferrucci & Fabbri, 2018). In addition, physical exercise has been shown to modulate aging-related changes, preventing muscle atrophy, maintaining cardiorespiratory fitness and cognitive function, enhancing metabolic activity and maintaining functional independence (Garatachea et al., 2015; Rebelo-Marques et al., 2018; Wleklik et al., 2020). However, the older adults are the population group with the highest rates of physical inactivity and sedentary behaviors. These factors further accentuate the negative age-related effects, and generates a series of consequences, not only medical, but also economic and social (Steffl et al., 2017; Wleklik et al., 2020).

Multicomponent training (MCT) is characterized by the combination at least 3 types of training such as strength, aerobic, balance, coordination, and flexibility training. Given the fundamental role of physical exercise in healthy aging, it is essential to know if MCT is effective in improving physical performance and therefore may be useful to reduce the incidence of falls and prevents disability, morbidity, and early mortality (Fragala et al., 2019; Garatachea et al., 2015). The latest international consensus of experts on exercise in the older adults recommends the implementation of MCT programs as one the best strategy for improving gait, balance, and strength, as well as reducing the of falls in older adults (Izquierdo et al., 2021). Previous information about MCT exists (Abdullah Alfadhel, Vennu, Alotaibi, Algarni, & Saad Bindawas, 2020; Borges-Machado et al., 2020; W. Bouaziz et al., 2016; Eduardo Lusa Cadore, Rodríguez-Mañas, Sinclair, & Izquierdo, 2013), but to date there is no meta-analysis studying the effectiveness of MCT in improving the physical performance in healthy older adults. The main objective of this systematic review and meta-analysis is to assess the effectiveness of MCT programs in improving physical performance in healthy older adults. The hypothesis of the study is that the MCT programs are effective in improving physical performance in healthy older adults.

METHODS

Experimental Approach to the Problem

The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist (Page et al., 2021). The systematic review and meta-analysis protocol were registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the code CRD42020186796.

In order to develop an accurate search strategy, the PICOS strategy was used (Methley, Campbell, Chew-Graham, McNally, & Cheraghi-Sohi, 2014). Population: healthy older adults; Intervention: multicomponent training (MCT); Comparison: no training;

Outcome: physical performance; Study design: randomized control trials (RCTs). Filters proposed by the Cochrane Collaboration for RCTs were combined with the search strategy ("Cochrane Handb. Syst. Rev. Interv.," 2019). Supplementary Appendix S1a shows the keywords included to develop the final search according to the PICOS strategy.

The Cochrane Library database, as well PubMed and Web of Science search engines were used in this systematic review and meta-analysis. In addition, a manual search was conducted, and the bibliography of other similar systematic reviews was checked in order to find potential studies. The final search was performed on September 1st, 2022. The complete search strategies are available on the *Supplementary Appendix S1b*.

Inclusion criteria: 1) randomized controlled trial study design, 2) adults aged >65, 3) healthy participants, 4) intervention group with a MCT, 5) comparison group with no training, 6) physical performance as outcome, and 7) English language. Exclusion criteria: 1) hospitalized or post-surgery participants, 2) sample with diabetes, cancer, cardiovascular disease, or other several acute/chronic conditions, 3) combination of MCT with other type of training, 4) training program duration shorter than 8 weeks, sufficient time to allow for changes due to the intervention to occur (Chen, He, Feng, Ainsworth, & Liu, 2021; Fragala et al., 2019; Valenzuela et al., 2019). Titles, abstracts, and full text were independently screened for potential inclusion by two researchers (PA and DG). In case of discrepancy, a third researcher (NL) was consulted for decision. Cohen's Kappa index was used to assess the inter-rater agreement (Landis & Koch, 1977). For every included study the following data was extracted: 1) author's last name, 2) year of publication, 3) sample size, 4) sample characteristics, 5) characteristics of the

MCT (type of training combined, volume, intensity, duration, and frequency), 6) control group characteristics, 7) outcomes, 8) main results, and 9) follow-up.

Procedure

The main outcome of this systematic review and meta-analysis was the physical performance, including various capacities such as muscle strength, gait speed, agility, and coordination. In order to study physical performance, it was decided to choose the most representative assessment tool for each study (Beaudart et al., 2019). Moreover, a subgroup meta-analysis for all the variables repeated in at least 3 studies was carried out.

The Risk of Bias tool (RoB) (Sterne et al., 2019) and the Physiotherapy Evidence Database (PEDro) scale (Maher, Sherrington, Herbert, Moseley, & Elkins, 2003) were used to evaluate the risk of bias and the methodological quality of the included studies. On one side, the RoB tool (Sterne et al., 2019), developed by the Cochrane Collaboration uses 7 domains to classify the included RCTs into “low”, “unclear”, or “high” risk of bias depending on the publication bias (sequence generation and allocation sequence concealment), performance bias (blinding participants and personnel), detection bias (blinding outcome assessor), attrition bias (incomplete data), reporting bias (selecting outcome reporting), and other bias (e.g. sample size). While, the PEDro scale (Maher et al., 2003) is an scale with 11 items evaluating the external validity (item 1), the internal validity (items 2-9), and the generalizability (items 10-11) of the RCT.

Qualitative analysis

In order to summarize the results taking into account the methodological quality of the studies, a best-evidence synthesis was applied. This rating system consists of three levels and takes into account the number, methodological quality through the PEDro score and consistency of outcomes of the studies: A) "strong evidence" is considered when consistent results are found in multiple (≥2) high-quality studies (PEDro score ≥4); B) "moderate evidence" is considered when consistent results are found in one high quality study and at least one low-quality study (PEDro score <4), or in multiple (≥2) low-quality studies; C) "insufficient evidence" is considered when consistent results are found in only one study available or inconsistent findings in multiple (≥2) studies. Consistency of the results was considered if at least 50% of the studies showed significant results in the same direction (Kampshoff et al., 2014; Kollen et al., 2009).

Statistical Analyses

The RevMan Manager 5.3 software (The Cochrane Collaboration, 2012) was used to perform the meta-analysis. For all studies, the sample size, post-intervention means, and standard deviations (SD) were introduced on the software. If any SD was missing, it was obtained from the confidence interval (CI). The corresponding author was contacted by email if any of the studies did not report some of the required data. The outcomes assessed were expressed as continuous. The articles that analyzed more than one comparison group were included in the meta-analysis individually as if they were different studies. A random-effects model was used as the study methodology differed between the articles included (DerSimonian & Laird, 1986). In addition, the effect measure was reflected as the mean difference (MD). However, in the cases where different tools and procedures were used to assess the variables, standard mean difference (SMD) was chosen. The overall effect size was calculated with a 95% CI.

Heterogeneity was classified as “small” (I2<25%), “moderate” (I2 25-75%), or “high” (I2>75%) (J. P T Higgins, 2003). In order to assess the individual weight of each study on the overall result, every study was removed one by one. Lastly, a funnel plot visual interpretation was performed for all outcomes in order to investigate a possible publication bias.

RESULTS

Study Selection

The search strategy found 530 studies (Cochrane Library: 206; PubMed: 141; Web of Science: 183). Three additional studies were also included after performing the manual search. After removing duplicates, a total of 294 studies were initially considered to be included. Two hundred and twenty-four articles were excluded after screening the titles and abstracts for not meeting the inclusion criteria. After assessing the full-text, 51 articles were excluded. After reading the full-text, 19 studies met the inclusion criteria for the qualitative analysis. Six studies dropped out from the meta-analysis for not presenting the required data after contacting with the corresponding authors. Finally, 13 articles were included in the quantitative synthesis, involving a total sample of 808 participants. The analysis of inter-observer agreement showed a Cohen’s Kappa index of k=0.74 categorized as “substantial” agreement (Landis & Koch, 1977). *Figure 1* presents the PRISMA 2020 flow diagram.

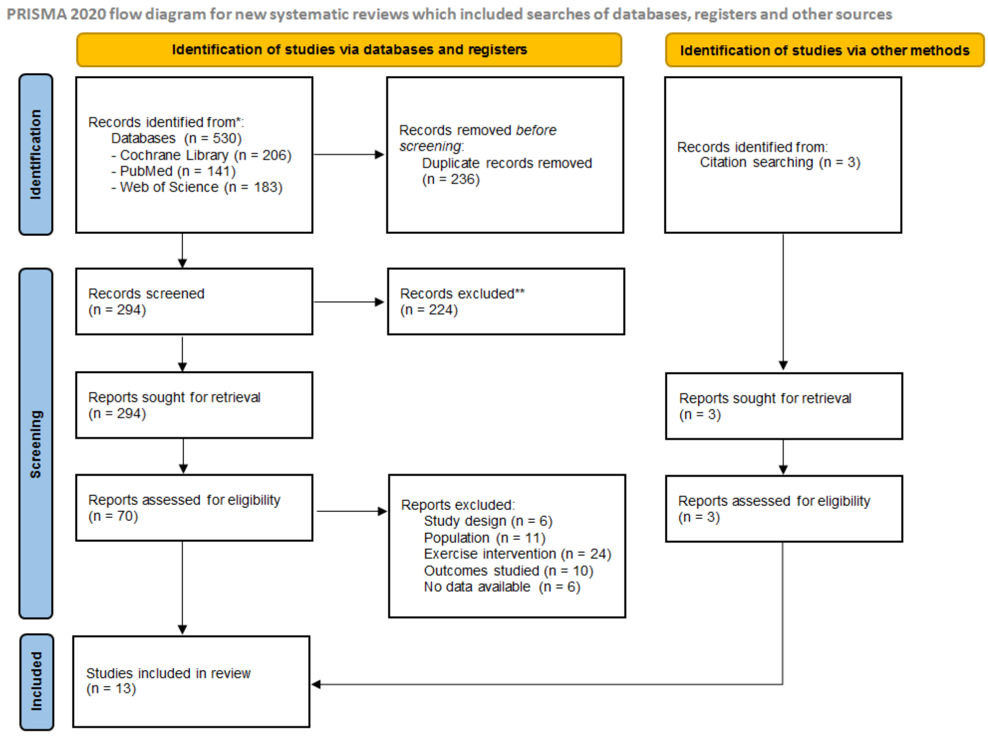

Figure 7. PRISMA 2020 flow diagram.

Study Characteristics

Table 1 summarizes the sample characteristics of the 13 included articles. A total of 808 older adults were included in this qualitative analysis. Most of the articles analyzed men and women, except in 3 articles (Carvalho, Marques, & Mota, 2009; Monteiro, Bartolomeu, Forte, & Carvalho, 2019; Puggaard, 2003b) where the sample was only women. One article did not report the gender of the participants (Millor et al., 2014). Approximately 70% of the participants were women. The sample size varied between 19 (Millor et al., 2014) and 115 (Binder et al., 2002) individuals, with an average age between 69.0 (Carvalho et al., 2009) and 91.9 years old (Eduardo L. Cadore et al., 2014).

In terms of the duration of the interventions, the training programs varied from 9 (F. Toraman & Şahin, 2004) to 36 weeks (Mulasso, Roppolo, Liubicich, Settanni, &

Rabaglietti, 2015), with an average of 21.30 (±9.60) weeks. The frequency of the training programs varied from 2 (Arrieta et al., 2019, 2018; Eduardo L. Cadore et al., 2014; Carvalho et al., 2009; Makizako et al., 2012; Millor et al., 2014; Mulasso et al., 2015; Puggaard, 2003a) to 5 (Tarazona-Santabalbina et al., 2016) sessions per week, being 2 sessions/week the most frequent. All 13 MCT training programs included aerobic training, resistance training, balance training, except the study of Taroman et al. that did not included balance training (F. Toraman & Şahin, 2004). Furthermore, 11 studies included stretching, and 4 coordination training. The intensity of the training sessions ranged from moderate to high-intensity. Finally, regarding the study variables related to physical performance (Arrieta et al., 2018; Binder et al., 2002; Eduardo L. Cadore et al., 2014; Carvalho et al., 2009; Monteiro et al., 2019; Mulasso et al., 2015; Puggaard, 2003b; Tarazona-Santabalbina et al., 2016; F. Toraman & Şahin, 2004), upper (Arrieta et al., 2018; Carvalho et al., 2009; Monteiro et al., 2019; F. Toraman & Şahin, 2004) and lower limb strength (Ansai, Aurichio, Gonçalves, & Rebelatto, 2016; Arrieta et al., 2018; Eduardo L. Cadore et al., 2014; Carvalho et al., 2009; Millor et al., 2014; Monteiro et al., 2019; F. Toraman & Şahin, 2004), walking speed (Eduardo L. Cadore et al., 2014; Makizako et al., 2012; Puggaard, 2003b), and aerobic capacity (Arrieta et al., 2018; Carvalho et al., 2009; Monteiro et al., 2019; F. Toraman & Şahin, 2004) were measured. The characteristics of the training protocols are summarized on *Supplementary Appendix S2*.

Table 1. Sample characteristics of the studies included in the quantitative analysis.

Study	**Population**				**Training Components**
	N (MCT/CG)	**Gender (M/F)**	**Age ± SD**	**BMI ± SD**	

Ansai, 2016	45 (22/23)	M/F (13/32)	82.4 ± 2.4	28.1 ± 4.5	AT, RT, BT, ST
Arrieta, 2018	92 (45/47)	M/F (16/76)	84.9	28.2 ± 5.3	AT, RT, BT, ST
Arrieta, 2019	112 (57/55)	M/F (33/79)	84.9	28.2 ± 5.3	AT, RT, BT, ST
Binder, 2002	115 (66/49)	M/F (55/60)	83 ± 4	26.9 ± 4.5	AT, RT, BT, ST; CT
Cadore, 2014	24 (11/13)	M/F (7/17)	91.9 ± 4.1	NR	AT, RT, BT, ST
Carvalho, 2009	57 (32/25)	F	69.0	27.28 ± 2.91	AT, RT, BT, ST, CT
Makizako, 2012	47 (24/23)	M/F (24/23)	76.0	NR	AT, RT, BT, ST
Millor, 2014	19 (8/11)	NR	91.9 ± 4.1	NR	AT, RT, BT
Monteiro, 2019	40 (20/20)	F	68.6	31.25 ± 5.97	AT, RT, BT, ST
Mulasso, 2015	104 (53/51)	M/F (23/81)	83.0	26.3 ± 5.2	AT, RT, BT, ST, CT
Puggaard, 2003	51 (43/52)	F	>65	NR	AT, RT, BT, CT
Tarazona-Santabalbina, 2016	82 (40/42)	M/F (38/44)	69.4	29.9 ± 5.6	AT, RT, BT, ST
Toraman, 2004	20 (9/11)	M/F (17/3)	79.9	29.7 ± 3.7	AT, RT, ST

MCT: multocomponent training; CG: control group; RT: resistance training; WG: walking group; M: male; F: Female; NR: no reported; SD: standard deviation; BMI: Body Mass Index; AT: aerobic training; RT: resistance training; BT: balance training; ST: stretching training; CT: coordination training

Methodological Quality

Figure 2a and *Figure 2b* show the RoB tool summary and graph respectively. Eleven studies had issues with the participants and personnel blinding, and 6 with the assessor blinding. The average score for the PEDro scale across the included studies was 5.84 points out of 10, which can be interpreted as a "fair" methodological quality *(Supplementary Appendix S3)* (Cashin & McAuley, 2020).

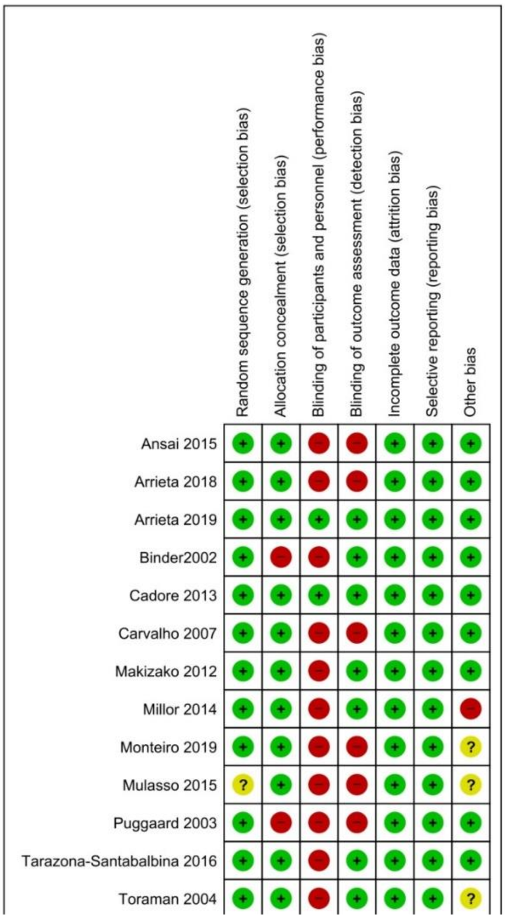

Figure 2a. Risk of bias summary.

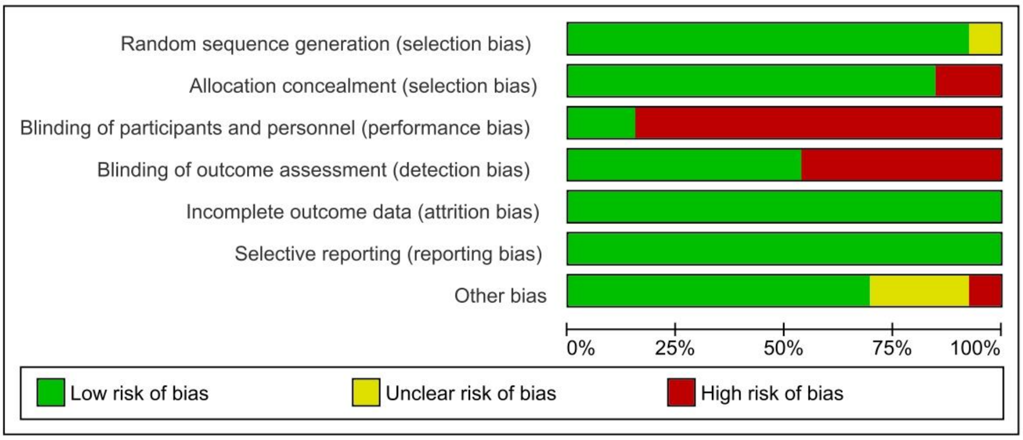

Figure 2b. Risk of bias graph.

Qualitative Analysis

Best-evidence synthesis is summarized in *Table 2.* Level of evidence of MCT for improving physical performance is considered “strong” in every of the functional tests.

Table 2. Best-evidence synthesis.

	N	**N+**	**N-**	**N0**	**LoE**
PP	13	7	0	6	A
SPPB	3	3	0	0	A
TUG	6	3	0	3	A
WS	7	5	0	2	A
LLS	7	5	0	2	A
ULS	4	3	0	1	A
AC	4	3	0	1	A

PP, Physical Performance; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go test; WS, Walking Speed; LLS, Lower Limb Strength; ULS, Upper Limb Strength; AC, Aerobic Capacity; N, total of studies; N+, number of studies showing statistically significant results in favor of MCT; N-, number of studies not showing statistically significant differences; N0, number of studies showing statistically significant results against MCT; LoE, Level of Evidence: A, strong evidence; B, moderate evidence; C, insufficient evidence.

Quantitative Analysis

The primary outcome assessed was physical performance by using the *Timed Up and Go (TUG)* test (Eduardo L. Cadore et al., 2014; Carvalho et al., 2009; Monteiro et al., 2019; Mulasso et al., 2015; F. Toraman & Şahin, 2004), the *Short Physical Performance Battery (SPPB)* (Arrieta et al., 2019, 2018; Tarazona-Santabalbina et al., 2016), the *Physical Performance Test (PPT)* (Binder et al., 2002; Puggaard, 2003b), the walking speed (Makizako et al., 2012), the *30-seconds chair-stand test (30''CST)* (Millor et al., 2014), and the *5-times sit-to-stand test (5SST)* (Ansai et al., 2016). The complete summary of the baseline and post-intervention data is reported in the *Supplementary Appendix S4.*

The comparison of MCT against no training *(Figure 3)* included 13 interventions with a total sample size of 848 participants, 430 for the MCT group and 418 for the control group. The overall SMD was 0.78 [95% CI, 0.55 to 1.00] and an overall effect of Z=6.84 ($p<0.01$). The heterogeneity showed by the I^2 statistic was moderate (I^2=54%). In order to investigate this heterogeneity, all studies were removed once from the analysis, but the heterogeneity did not vary.

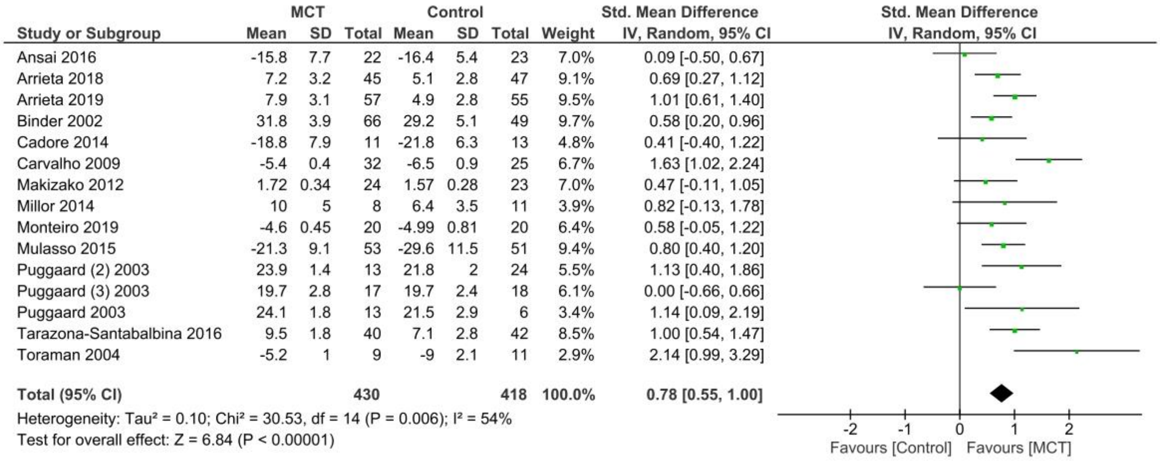

Figure 3. Effectiveness of MCT on physical performance.

The subgroup meta-analysis comparing MCT and a no training group assessed with the SPPB *(Figure 4)* included 3 studies with a total sample size of 286 participants, 142 for the MCT group and 144 for the non-training group. The overall MD was 2.52 [95% CI, 1.89 to 3.16] and an overall effect of Z=7.77 (p<0.01). Results showed no heterogeneity (I^2=0%).

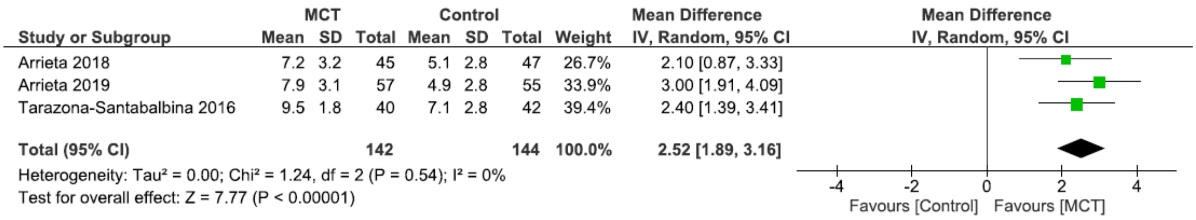

Figure 4. Effectiveness of MCT on Short Physical Performance Battery (SPPB).

The subgroup meta-analysis comparing MCT against no training with the TUG test *(Figure 5)* included 6 studies with a total sample size of 337 participants, 170 for the MCT group and 167 for the non-training group. The overall SMD was 0.90 [95% CI, 0.44 to 1.35] and an overall effect of Z=3.83 (p<0.001). The heterogeneity showed by the I^2 statistic was moderate (I^2=71%). In order to investigate this heterogeneity, all studies were removed once from the analysis, but the heterogeneity did not vary. When the studies conducted by Carvalho et al. (Carvalho et al., 2009) and Toraman et al. (F. Toraman & Şahin, 2004) were removed, the heterogeneity dropped to 0%.

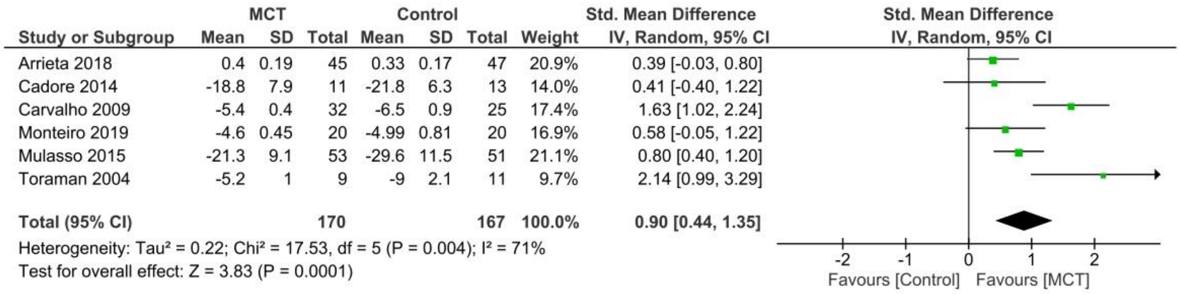

Figure 5. Effectiveness of MCT on Timed Up and Go Test (TUG).

The subgroup meta-analysis comparing MCT against no training evaluated with the walking speed *(Figure 6)* included 4 studies with a total sample size of 251 participants, 119 for the MCT group and 132 for the control group. The overall SMD was 0.75 [95% CI, 0.32 to 1.19] and an overall effect of Z=3.40 ($p<0.01$). The heterogeneity showed by the I^2 statistic was moderate (I^2=58%). In order to investigate this heterogeneity, all studies were removed once from the analysis. When the study conducted by Cadore et al. (Eduardo L. Cadore et al., 2014) was removed, the heterogeneity dropped to 0%.

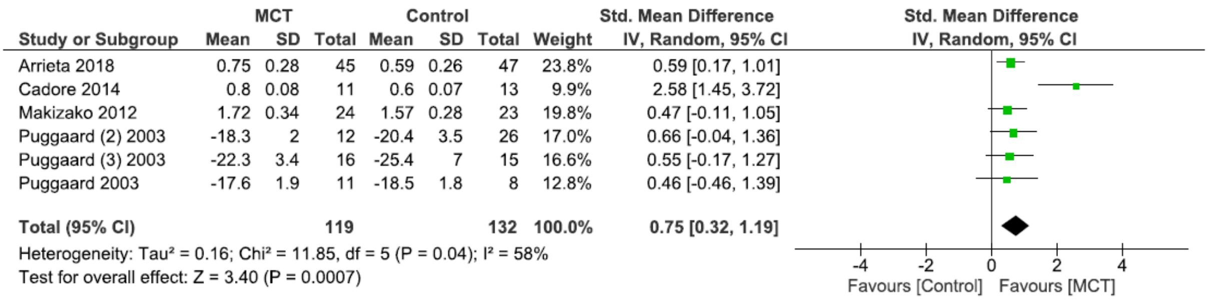

Figure 6. Effectiveness of MCT on Walking speed.

The subgroup meta-analysis assessing lower limb strength was assessed with the *30-seconds chair stand test (30''CST)*, except in the study conducted by Ansai et al. (Ansai et al., 2016) that performed the *5-times sit to stand test (5SST)*. The comparison of MCT against no training *(Figure 7)* included 7 studies with a total sample size of 294 participants, 147 for the MCT group and 147 for the non-training group. The overall SMD was 1.14 [95% CI, 0.43 to 1.85] and an overall effect of Z=3.14 ($p<0.01$). The heterogeneity showed by the I^2 statistic was high (I^2=86%). In order to investigate this heterogeneity, studies conducted by Carvalho et al. (Carvalho et al. 2009) and Toraman et al. (F. Toraman & Şahin, 2004) were removed and the heterogeneity dropped to 0%.

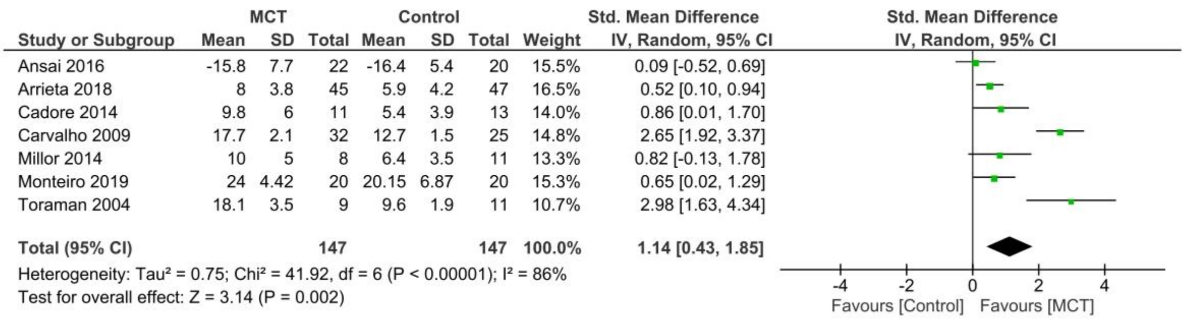

Figure 7. Effectiveness of MCT on Lower limb strength.

Upper limb strength was assessed with the *Arm-Curl Test (ACT)* in all the studies. The comparison of MCT against no training *(Figure 8)* included 4 studies with a total sample size of 209 participants, 106 for the MCT group and 103 for the non-training group. The overall MD was 4.53 [95% CI, 2.57 to 6.50] and an overall effect of Z=4.53 ($p<0.01$). The heterogeneity showed by the I^2 statistic was moderate (I^2=70%). When the study by Toraman et al. (F. Toraman & Şahin, 2004) was removed, the heterogeneity dropped to 0%.

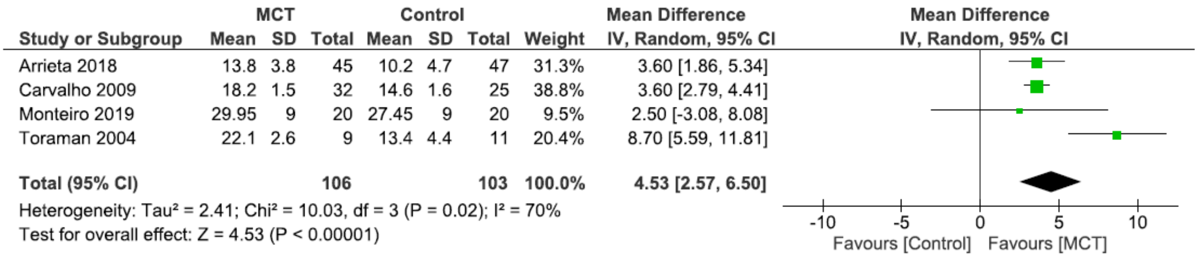

Figure 8. Effectiveness of MCT on Upper limb strength.

Aerobic capacity was assessed with the *6-minutes walking test (6MWT)* in all the studies except Monteiro et al. (Monteiro et al., 2019) that used the *2-minute step test (2'ST).* The comparison of MCT against no training *(Figure 9)* included 4 studies with a total sample size of 209 participants, 106 for the MCT group and 103 for the non-training group. The overall SMD was 0.74 [95% CI, 0.17 to 1.30] and an overall effect of Z=2.57 (p=0.01). The heterogeneity showed by the I^2 statistic was moderate (I^2=70%). When the study conducted by Toraman et al. (F. Toraman & Şahin, 2004) was removed, the heterogeneity dropped to 21%.

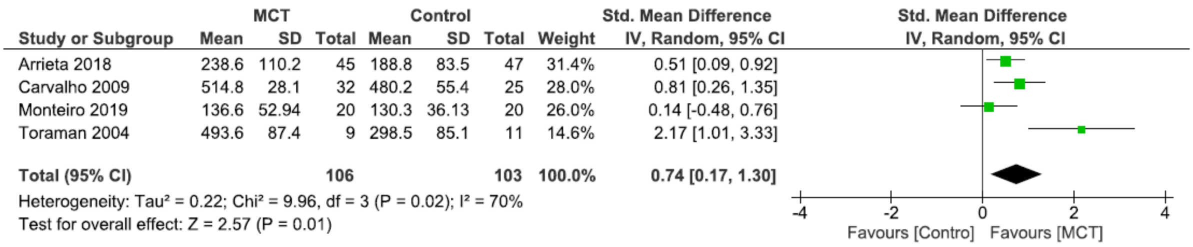

Figure 9. Effectiveness of MCT on Aerobic capacity.

Complete sensitivity analysis and funnel plots are also available in the *Supplementary Appendix S5* and *S6*.

DISCUSSION

This is the first meta-analysis to collect the current evidence from RCTs on the effectiveness of MCT programs in improving physical performance in healthy older adults. This work collects evidence from 13 articles, with a total of 808 participants involved. In general, the hypothesis of the study has been confirmed, as MCT is effective in improving physical performance in older adults. Regarding the characteristics of the different interventions, it should be noted that all the interventions lasted 12 weeks or more, except for the study by Toraman et al. (F. Toraman & Şahin, 2004) which lasted 9 weeks. Longer training periods (>12 weeks) may be more effective than shorter interventions (Fragala et al., 2019), however, the study by Toraman et al. (F. Toraman & Şahin, 2004) still showed significant differences in favor of MCT in all its study variables. This could be interesting because it may show that shorter training periods could enough to improve physical fitness. Nevertheless, to confirm this statement, more studies analyzing the effects on physical performance of shorter (8-12 weeks) duration MCT training programs should be carried out in order to better know which the minimum effective dose is. On the other hand, only 2 studies included in this systematic review assessed the outcomes at follow-up 6 and 9 weeks after post-intervention assessment (Ansai et al., 2016; Carvalho et al., 2009). In accordance with Toraman et al. (N. F. Toraman, 2005; N. F. Toraman & Ayceman, 2005), both studies reported a decrease in physical performance levels during detraining period. The durability of the effects have not been systematically reviewed in older adults, however, Sousa et al. (Sousa et al., 2019) suggested that most of training-induced gains were reversed after 4 weeks of detraining in young adults. Taking into account the early loss of physical performance associated with lack of physical activity or sedentary lifestyle in older adults, MCT should be maintained over longer periods in order to maintain training-induced gains in physical performance showed in meta-analysis.

In terms of physical capabilities trained, the majority of studies included resistance, and balance training, these being fundamental in the improvement of physical performance (Valenzuela et al., 2018). The main objective of resistance training is to improve muscle strength. As previously mentioned, muscle strength assessment is currently the main diagnostic tool for sarcopenia (Cruz-Jentoft et al., 2019). In addition, a decrease in muscle strength has been related to a worse ability to perform activities of daily living as well as a predictor of future adverse events (Wang, Yao, Zirek, Reijnierse, & Maier, 2020). Results about lower limb and upper limb muscle strength are in accordance with the meta-analysis from Guizelini et al. (Guizelini, de Aguiar, Denadai, Caputo, & Greco, 2018) suggesting that MCT improves strength as much as isolated resistance training programs. In turn, balance training alone has also evidenced that is effective in improving the risk of falls (Lesinski, Hortobágyi, Muehlbauer, Gollhofer, & Granacher, 2015).

Additionally, all of the 13 studies also included aerobic training. However, only four studies reported aerobic capacity outcomes measured by functional tests as 6MWT or 2'ST. Positive effects of aerobic training in older adults have been widely reported in both heart disease patients (Hollings, Mavros, Freeston, & Fiatarone Singh, 2017) and healthy older adults (W. Bouaziz et al., 2016; Huang, Shi, Davis-Brezette, & Osness, 2005). The systematic review conducted by Huang et al. (Huang et al., 2005) assessed the effects of endurance training on resting heart rate in older adults. They showed an overall effect of -0.58 favoring endurance group. Bouaziz et al. (W. Bouaziz et al., 2016) showed an improvement of 1.72 on peak oxygen uptake among healthy older adults. Aerobic training have showed benefits for health outcomes as quality of life, risk of heart disease, cognitive function, lifespan or blood pressure (W. Bouaziz et al., 2016; Walid Bouaziz, Schmitt, Kaltenbach, Geny, & Vogel, 2015). The present meta-analysis have found an aerobic capacity improvement associated with MCT training, suggesting that MCT could also lead to similar health benefits on older adults as other aerobic training programs previously mentioned (W. Bouaziz et al., 2016; Walid Bouaziz et al., 2015; Huang et al., 2005).

Regarding the results of the meta-analysis, physical performance showed significant differences in favor of the MCT. These results are consistent with those of previous studies, such as Borges-Machado et al. (Borges-Machado et al., 2020), that conducted a meta-analisys in older adults with dementia, and with Bouaziz et al. (W. Bouaziz et al., 2016), that included observational studies in their review. Moreover, the same results were obtained in two previous systematic reviews conducted by Cadore et al (Eduardo Lusa Cadore et al., 2013) and Abdullah et al. (Abdullah Alfadhel et al., 2020), that did not perform a meta-analysis. Finally, the results agree as well as with the National Strength and Conditioning Association (NSCA) recommendations for older adults, that claim the use of MCT in old healthy people in order to improve their health status (Fragala et al., 2019). Similar results have been obtained by studying separately the variables of upper and lower limb strength, walking speed and aerobic capacity. All these variables have been related to a lower future risk of mobility impairments, falls, institutionalization, care dependency, hospitalization, and mortality (Applebaum et al., 2017; Beaudart et al., 2019; Pavasini et al., 2016; Shumway-Cook, Brauer, & Woollacott, 2000; Volpato et al., 2011).

More specifically, Harvey et al. (Harvey et al., 2018) conducted a huge cohort study involving 10411 participants and follow-up periods between 8.7 and 10.9 years. They found a strong association between risk of falls and fractures, and physical performance outcomes. Outcomes measured in this meta-analysis, as walking speed and upper limb strength showed a Hazard ratio HR of 0.85 [95% CI, 0.79 to 0.90] and 0.77 [95% CI, 0.72 to 0.82] respectively. It means that lower walking speed and lower upper limb strength are strongly associated with major non-traumatic fractures. Results of the present meta-analysis showed that MCT can improve both walking speed and upper limb strength in healthy older adults, and could protect them from adverse events as osteoporotic fractures.

Pavasini et al. (Pavasini et al., 2016) also studied the association between SPPB score and all-cause mortality. They carried out a meta-analysis involving 16534 participants with a mean age of 76 years. Values of 0-3 [Odds ratio OR 3.25; 95%CI 2.86-3.79)], 4-6 [OR 2.14 95%CI 1.92-2.39], and 7-9 [OR 1.5 95%CI 1.32-1.71] in SPPB were associated with all-cause mortality when comparing them to 10-12 SPPB scores. Results of the current meta-analysis showed that MCT programs improve significantly SPPB scores, which could have a protective effect for all-cause mortality based on current scientific evidence available.

The present meta-analysis also showed that MCT programs decrease TUG time in healthy older adults. Jeong et al. (Jeong et al., 2019) studied the TUG test as predictor of fracture in a big cohort of more than a million 66 years old population. They found older adults with TUG score ≥10 are 23% more likely to suffer a hip fracture in comparison with those with TUG score <10. Moreover, Chua et al. (Chua, Lim, Lin, Yuan, & Koh, 2020) found older adults with higher TUG scores were 3 times more likely to all-cause mortality in a cohort of 13765 adults with mean age of 74. Once more, MCT could have a protective effect for all-cause mortality associated with a TUG time reduction.

In addition, our meta-analysis showed that MCT improved lower limb strength, which has been showed to protect older adults against adverse events. In fact, García-Hermoso et al. (García-Hermoso et al., 2018) performed a meta-analysis with nearly 2 million older adults and found that those with higher lower limb strength had 14% lower risk of death. Moreover, comparing MCT with other types of training, specifically resistance training, Meereis-Lemos et al. (Meereis Lemos, Guadagnin, & Mota, 2020) found better results for MCT.

Taking into account the guidelines for sarcopenia, people over 65 years of age should be assessed from muscle strength. For this assessment, evidence recommend the use of handgrip strength, or the chair rise test. It is surprising that the handgrip, being a widely studied marker (Cruz-Jentoft et al., 2019), has only been assessed in 2 of the 13 studies included (Arrieta et al., 2018; Eduardo L. Cadore et al., 2014). Despite not meeting the minimum number of studies required for inclusion in the meta-analysis by subgroups, the studies show contradictory results. Cadore et al. (Eduardo L. Cadore et al., 2014) found significant improvements in grip strength, while Arrieta et al. (Arrieta et al., 2018) obtained a significant decrease in the grip strength.

Although the results obtained from the different subgroups of the meta-analysis show significant improvements in functional capacity, the differences obtained between the different functional tests are surprising. If we focus on the recommendations for the assessment of physical performance in older adults (Beaudart et al., 2019), it should be assessed using the SPPB, the 5CRT, gait speed or the TUG. When comparing the results obtained by these tests, disparity is found between them. Specifically, the results obtained using the SPPB are higher than the other tests, despite including a smaller number of studies in the analysis. Taking into account the evidence on the effectiveness of training in improving functionality versus non-training, it is pertinent to question the validity of the different tests in the assessment of physical performance in a MCT program.

Study Limitations

This study is not without limitations. It is important to comment on the heterogeneity of the results of each study, as well as the intrinsic characteristics of the studies. These differences are mainly related to the training protocols, in which the duration of the program, as well as the combined physical capacities (strength, resistance, balance, and coordination) vary notably. Furthermore, there is no agreement in the frequency, volume, and intensity of the exercises, as well as in the selection of the exercises themselves. In addition, we are aware that the search strategy itself could have left out some studies in which the intervention consisted of 3 or more components, but the authors did not refer to it as MCT. With regard to the characteristics of the sample, it should be noted that, despite the fact that all the people were over 65 years old, in some of the studies the age of the participants was even over 85 years old. Moreover, we must reflect that, although all the studies were randomized, some baseline values of the study variables were different between the intervention group and the control group. Finally, we should point out that, although we included the outcomes of falls and “quality of life” in our search strategy, none of the final studies evaluated them. Thus, they have not been discussed in this study.

PRACTICAL APPLICATIONS

The results of this meta-analysis confirm that MCT is a valid tool to improve physical performance in healthy older adults. Specifically, the MCT improves general functionality, strength in upper and lower extremities, walking speed and aerobic capacity. In this sense, the implementation of MCT programs should be encouraged as an effective tool in the prevention of conditions as prevalent in the older adult as frailty. The differences in physical performance obtained by the different assessment tests suggest the need to standardize methodologies to reliably assess improvements in physical fitness in older adults.

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Supplementary Appendix S1a. Keywords used for the search strategy.

Population	Intervention	Outcomes
Aged	Multicomponent training	Physical fitness
Old people	Multicomponent exercise	Physical function
Elderly		Functionality
Aging		Functional capacity
Older people		Functional ability
Older adults		Functional parameters
Old adults		Functional capabilities
Frail		Performance
Senior		Fitness
Geriatric		Strength
		Resistance
		Endurance
		Balance
		Stability
		Agility
		Mobility
		Gait
		Speed
		Locomotion
		Fall
		Falling

Handgrip
SPPB
Tandem
TUG
Quality of life

Supplementary Appendix S1b: Complete literature search.

PubMed Search Formula

#1 (aged [mh] OR aged OR "old people" OR "older people" OR "older adults" OR "old adults" OR elderly OR senior OR geriatric OR frail)

#2 ("multicomponent training" OR "multi-component training" OR "multicomponent exercise" OR "multi-component exercise")

#3 (physical fitness [mh] OR physical fitness OR functionality OR Performance OR Strength OR Resistance OR Endurance OR balance OR stability OR agility OR mobility OR Gait OR Speed OR Locomotion OR fall OR Handgrip OR SPPB OR Tandem OR TUG OR "Timed up and go" OR "quality of life")

#4 (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [TiAb] OR placebo [TiAb] OR clinical trials as topic [mesh: noexp] OR randomly [TiAb] OR trial [Ti]) NOT (animals [mh] NOT humans [mh])

#6 #1 AND #2 AND #3 AND #4

Results: 141

Date: 01/09/2022

Cochrane Library Search Formula

#1 MeSH descriptor: [Aged] explode all trees

#2 (aged):ti,ab,kw

#3 ("old people"):ti,ab,kw

#4 ("old adults"):ti,ab,kw

#5 ("older people"):ti,ab,kw

#6 ("older adults"):ti,ab,kw

#7 (ageing):ti,ab,kw

#8 (frail):ti,ab,kw

#9 (elderly):ti,ab,kw

#10 (senior):ti,ab,kw

#11 (geriatric):ti,ab,kw

#12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

#13 MeSH descriptor: [Physical Fitness] explode all trees

#14 ("physical function"):ti,ab,kw

#15 (functionality):ti,ab,kw

#16 ("functional capacity"):ti,ab,kw

#17 ("functional ability"):ti,ab,kw

#18 ("functional parameters"):ti,ab,kw

#19 ("functional capabilities"):ti,ab,kw

#20 (performance):ti,ab,kw

#21 (strength):ti,ab,kw

#22 (endurance):ti,ab,kw

#23 (balance):ti,ab,kw

#24 (resistance):ti,ab,kw

#25 (stability):ti,ab,kw

#26 (agility):ti,ab,kw

#27 (mobility):ti,ab,kw

#28 (speed):ti,ab,kw

#29 (gait):ti,ab,kw

#30 (locomotion):ti,ab,kw

#31 (falls):ti,ab,kw

#32 (falling):ti,ab,kw

#33 (handgrip):ti,ab,kw

#34 (SPPB):ti,ab,kw

#35 (Tandem):ti,ab,kw

#36 (TUG):ti,ab,kw

#37 ("quality of life"):ti,ab,kw

#38 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37

#39 (“multicomponent training”):ti,ab,kw

#40 (“multi-component training”):ti,ab,kw

#41 (“multicomponent exercise”):ti,ab,kw

#42 (“multi-component exercise”):ti,ab,kw

#43 #39 OR #40 OR #41 OR #42

#46 #12 AND #38 AND #43

Results: 206

Date: 01/09/2022

Web of Science Search Formula

#1 ALL=(aged OR “old people” OR “older people” OR “older adults” OR “old adults” OR elderly OR senior OR geriatric OR frail)

#2 ALL=("multi-component training" OR "multicomponent training" OR "multi-component exercise" OR "multicomponent exercise")

#3 ALL=(“physical fitness” OR functionality OR Performance OR Strength OR Resistance OR Endurance OR balance OR stability OR agility OR mobility OR Gait OR Speed OR Locomotion OR fall OR Handgrip OR SPPB OR Tandem OR TUG OR "Timed up and go" OR "quality of life")

#4 TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*)

#6 (TS=#1 AND #2 AND #3 AND #4)

Results: 183

Date: 01/09/2022

Supplementary Appendix S2: Additional characteristics of the MCT protocols.

Study	Frequency	Components	Duration (min)	Intensity	Sets x Reps	Outcomes
Ansai, 2016	16 w 3 s/w	AT RT BT ST	20 15-20 10 5	60-80% HRR 14-17 RPE NR NR	NR	LLS: 5SST
Arrieta, 2018	12 w 2 s/w	AT RT BT ST	5-15 25 10 5	NR 40-70% 1RM NR NR	NR	ULS: ACT LLS: 30"CST PP: SPPB, TUG, WS AC: 6'WT
Arrieta, 2019	24 w 2 s/w	AT RT BT	5-15 25 10	NR 40-70% 1RM	NR	PP: SPPB

		ST	5	NR NR		
Binder, 2002	12 w 3 s/w	AT RT BT ST CT	30 NR NR NR NR	65-90% V02peak 65-100% 1RM NR NR NR	NR 2-3 x 6-12 NR NR NR	PP: PPT
Cadore, 2014	12 w 2 s/w	AT RT BT ST	5 20 10 5	NR 40-60% 1RM NR NR	NR NR x 8-10 NR NR	LLS: 30"CST PP: TUG, WS
Carvalho, 2009	32 w 2 s/w	AT RT BT ST	25 20 5 5	12-14 Borg 12-16 RPE NR	NR 2-3 x 8-15 NR	ULS: ACT LLS: 30"CST PP: TUG

		CT	5	NR NR	3-4 x 30- 40” NR	AC: 6’WT
Makizako, 2012	24 w 2 s/w	AT RT BT ST	30 20 30 10	60% HRmax NR NR NR	NR NR NR NR	PP: WS
Millor, 2014	12 w 2 s/w	AT RT BT	40	NR 40-60% 1RM NR	NR NR x 8-10 NR	LLS: 30”CST
Monteiro, 2019	32 w 3 s/w	AT RT BT ST	15-20 20-25 10 10	12-14 Borg NR NR NR	NR 1-3 x 8-15 NR NR	ULS: ACT LLS: 30”CST PP: TUG AC: 2’ST
Mulasso, 2015	36 w	AT	10	NR	NR	PP: TUG

	2 s/w	RT BT ST CT	20 15 10 20		3-4 x 5-12 NR NR NR	
Puggaard, 2003	32 w 2 s/w	AT RT BT CT	NR	48-82% HRmax	NR	PP: PPT, WS
Tarazona-Santabalbina, 2016	24 w 5 s/w	AT RT BT ST	10 40 10 5	NR 25-75% 1RM NR NR	NR 1-3 x 8-30 NR NR	PP: SPPB
Toraman, 2004	9 w 3 s/w	AT RT ST	70	50% HRR 50-80% 1RM NR	NR 1-3 x 8-12 NR	ULS: ACT LLS: 30"CST PP: TUG AC: 6'WT

w: week; s/w: sessions per week; AT: aerobic training; RT: resistance training; BT: balance training; ST: stretching training; CT: coordination training; RM: repetition maximum; RPE: rated perceived exertion; HRmax: maximum heart rate; HRR: heart rate reserve; LLS: lower limb strength; ULS: upper limb strength; PP: physical performance; AC: aerobic capacity; ST: stretching; ACT: arm curl test; 30''CST: 30-seconds chair stand test; 5SST: 5-times sit to stand test; SPPB: short physical performance battery; TUG: timed up and go test; PPT: physical performance test; WS: walking speed; 6'WT: 6-minutes walking test; 2'ST: 2-minutes step test; S&R: seat and reach test; NR: no reported

Table 2. PEDro scale.

Study	1	2	3	4	5	6	7	8	9	10	11	Total*
Ansai, 2016	1	1	1	1	0	0	0	1	1	1	1	7
Arrieta, 2018	0	1	1	1	0	0	0	0	0	1	1	5
Arrieta, 2019	1	1	1	1	0	0	1	0	0	1	1	6
Binder, 2002	1	1	0	1	0	1	1	0	0	1	1	8
Cadore, 2014	1	1	1	1	0	0	1	0	0	1	1	6
Carvalho, 2009	1	1	0	1	0	0	0	1	0	1	1	6
Makizako, 2012	1	1	0	1	0	0	1	1	0	1	1	7
Millor, 2014	1	1	0	0	0	0	1	0	1	1	1	5
Monteiro, 2019	1	1	0	0	0	0	0	1	1	1	1	6
Mulasso, 2015	1	1	0	1	0	0	0	1	1	1	1	7
Puggaard, 2003	1	0	0	1	0	0	0	0	0	1	1	3
Tarazona-Santabalbina, 2016	1	1	0	1	0	0	1	0	1	1	1	6
Toraman, 2004	1	1	0	1	0	0	0	1	0	0	1	4
Average*												**5.84**

* Item 1 is not used to calculate the PEDro score; 1: Inclusion/Exclusion Criteria; 2: Random Allocation of Participants; 3: Concealed Allocation; 4: Similarity Between Groups at Baseline; 5: Participant Blinding; 6: Therapist Blinding; 7: Assessor Blinding; 8: Fewer than 15% Dropouts; 9: Intention- to-Treat Analysis; 10: Between- Group Statistical Comparisons; 11: Point Measures and Variability Data.

Supplementary Appendix S4: Additional results of the studies.

Study	Outcome	MCT Group			Control Group		
		n	**PRE** *Mean (SD)*	**POST** *Mean (SD)*	n	**PRE** *Mean (SD)*	**POST** *Mean (SD)*
Ansai, 2016	LLS: 5SST (s)	22	18.9 (8.6)	15.8 (7.7)*+	23	16.0 (4.7)	16.4 (5.4)*
Arrieta, 2018	ULS: ACT (reps) LLS: 30"CST (reps) PP: SPPB (p) PP: TUG (m/s) PP: WS (m/s) AC: 6'WT (m)	45	13.1 (3.9) 7.6 (3.9) 6.0 (3.0) 0.42 (0.19) 0.66 (0.24) 244.7 (96.9)	13.8 (3.8)+ 8.0 (3.8)+ 7.2 (3.2)*+ 0.40 (0.19) + 0.75 (0.28)*+ 238.6 (110.2)	47	11.9 (4.1) 7.4 (4.1) 5.9 (2.7) 0.38 (0.16) 0.64 (0.24) 217.4 (93.8)	10.2 (4.7)* 5.9 (4.2)* 5.1 (2.8)* 0.33 (0.17)* 0.59 (0.26)* 188.8 (83.5)
Arrieta, 2019	PP: SPPB (p)	57	6.1 (3.1)	7.9 (3.1)*+	55	5.8 (2.7)	4.9 (2.8)*

Binder, 2002	PP: PPT (p)	66	28.4 (4.7)	31.8 (3.9)*+	49	28.3 (5.9)	29.2 (5.1)*
Cadore, 2014	LLS: 30”CST (reps) PP: TUG (s) PP: WS (m/s)	11	6.2 (4.1) 19.9 (8.0) 0.76 (0.07)	9.8 (6.0)*+ 18.8 (7.9)*+ 0.80 (0.08)	13	6.3 (3.4) 18.4 (5.1) 0.68 (0.06)	5.4 (3.9) 21.8 (6.3) 0.60 (0.07)*
Carvalho, 2009	ULS: ACT (reps) LLS: 30”CST (reps) PP: TUG (s) AC: 6’WT (m)	32	15.5 (2.3) 13.9 (1.6) 6.1 (0.7) 499.1 (44.7)	18.2 (1.5)*+ 17.7 (2.1)*+ 5.4 (0.4)*+ 514.8 (28.1)+	25	16.4 (1.9) 14.6 (1.6) 6.1 (0.9) 509.0 (64.8)	14.6 (1.6)* 12.7 (1.5)* 6.5 (0.9)* 480.2 (55.4)*
Makizako, 2012	PP: WS (m/s)	24	1.6 (0.4)	1.72 (0.34)+	23	1.6 (0.3)	1.57 (0.28)*
Millor, 2014	LLS: 30”CST	8	7.0 (3.0)	10.0 (5.0)+	11	5.8 (2.4)	6.4 (3.5)

	(reps)						
Monteiro, 2019	ULS: ACT (reps) LLS: 30"CST (reps) PP: TUG (s) AC: 2'ST (reps)	20	24.60 (9.08) 19.75 (4.35) 4.87 (0.91) 114.50 (53.56)	29.95 (9.01)*+ 24.00 (4.42)*+ 4.60 (0.45) 136.60 (52.94)*+	20	31.65 (10.20) 22.75 (6.77) 4.74 (0.75) 139.90 (41.04)	27.45 (9.00)* 20.15 (6.87) 4.99 (0.81) 130.30 (36.13)
Mulasso, 2015	PP: TUG (s)	53	25.0 (10.3)	21.3 (9.1)+	51	24.8 (9.6)	29.6 (11.5)
Puggaard, 2003	PP: PPT (p) PP: WS 30m (s)	13	22.9 (2.6) 19.1 (1.9)	24.1 (1.8) 17.6 (1.9)+	8	22.3 (2.1) 19.0 (1.7)	21.5 (2.9) 18.5 (1.8)*
Puggaard (2), 2003	PP: PPT (p) PP: WS 30m (s)	13	23.9 (1.9) 19.5 (2.2)	23.9 (1.4) 18.3 (2.0)*	26	23.4 (2.5) 20.9 (4.2)	21.8 (2.0)* 20.4 (3.5)
Puggaard (3),	PP: PPT (p)	17	18.8 (3.4)	19.7 (2.8)*	18	20.0 (3.1)	19.7 (2.4)

2003	PP: WS 30m (s)		27.0 (4.6)	22.3 (3.4)*+		26.3 (6.9)	25.4 (7.0)
Tarazona-Santabalbina, 2016	PP: SPPB (p)	40	8.6 (2.0)	9.5 (1.8)	42	8.6 (1.7)	7.1 (2.8)
Toraman, 2004	ULS: ACT (reps) LLS: 30"CST (reps) PP: TUG (s) AC: 6'WT (m)	9	17.4 (3.5) 10.6 (2) 7.2 (1.5) 447 (80.4)	22.1 (2.6)* 18.1 (3.5)* 5.2 (1)* 493.6 (87.4)*	11	14.2 (4.9) 10.3 (1.9) 9.1 (2.1) 302.9 (83.3)	13.4 (4.4) 9.6 (1.9) 9 (2.1) 298.5 (85.1)

LLS: lower limb strength; ULS: upper limb strength; PP: physical performance; AC: aerobic capacity; ACT: arm curl test; 30''CST: 30-seconds chair stand test; 5SST: 5-times sit to stand test; SPPB: short physical performance battery; TUG: timed up and go test; PPT: physical performance test; WS: walking speed; 6'WT: 6-minutes walking test; 2'ST: 2-minutes step test; *: $p < .05$, significantly different from baseline; +: $p < .05$, significantly different between groups after training.

Supplementary Appendix S5: Funnel Plots.

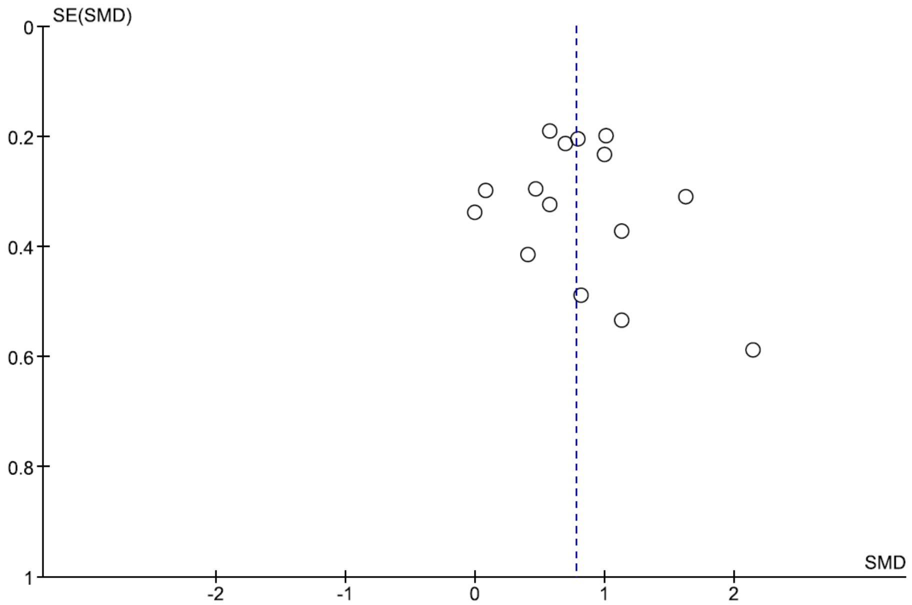

Figure 5a. Funnel plot of MCT on physical performance.

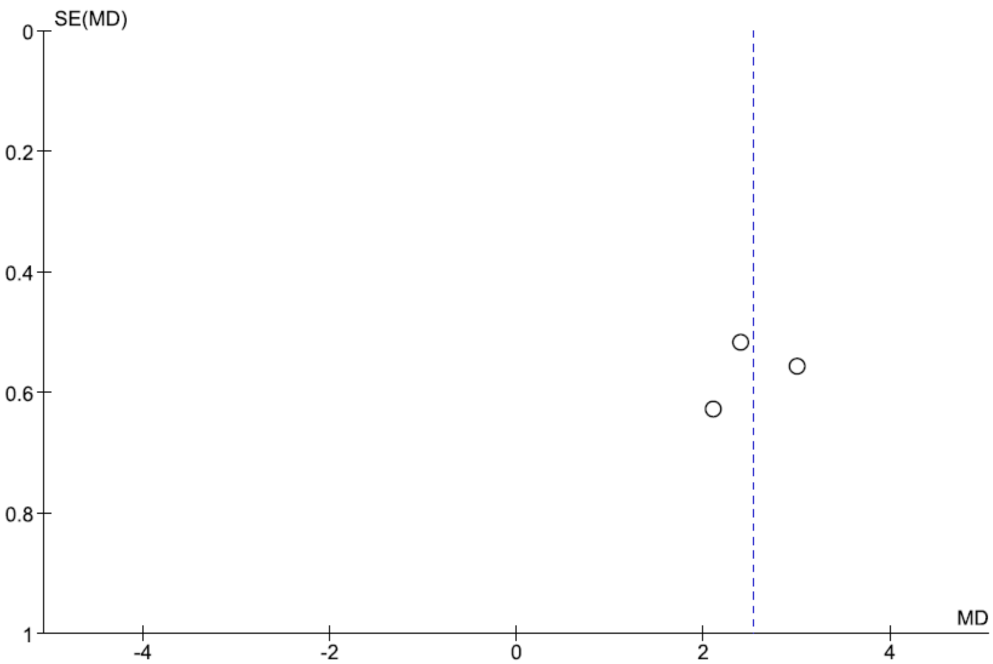

Figure S5b. Funnel plot of MCT on Short Physical Performance Battery (SPPB).

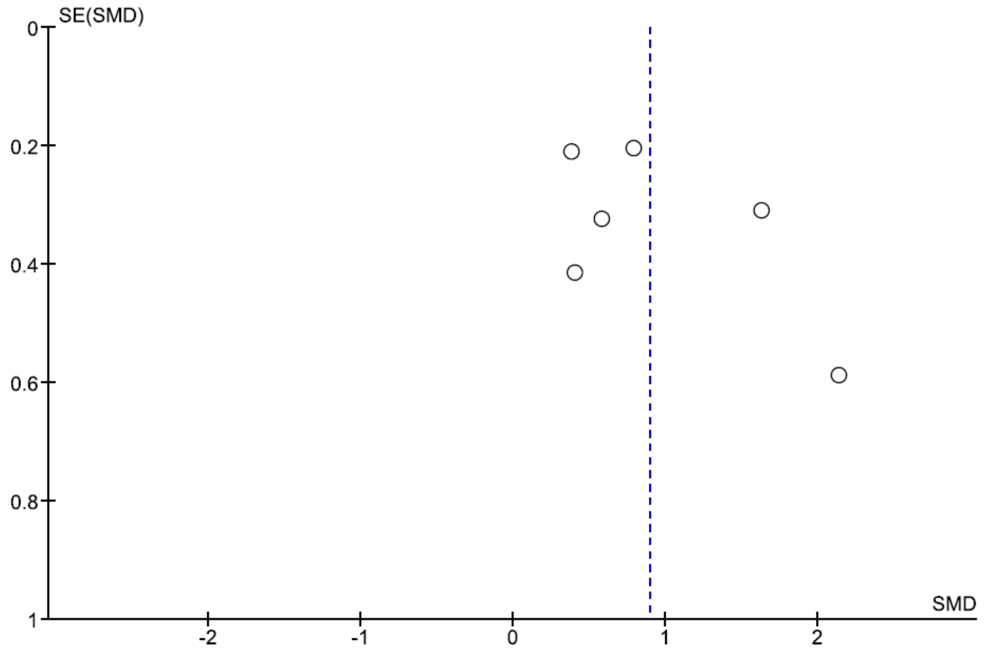

Figure S5c. Funnel plot of MCT on Timed Up and Go Test (TUG).

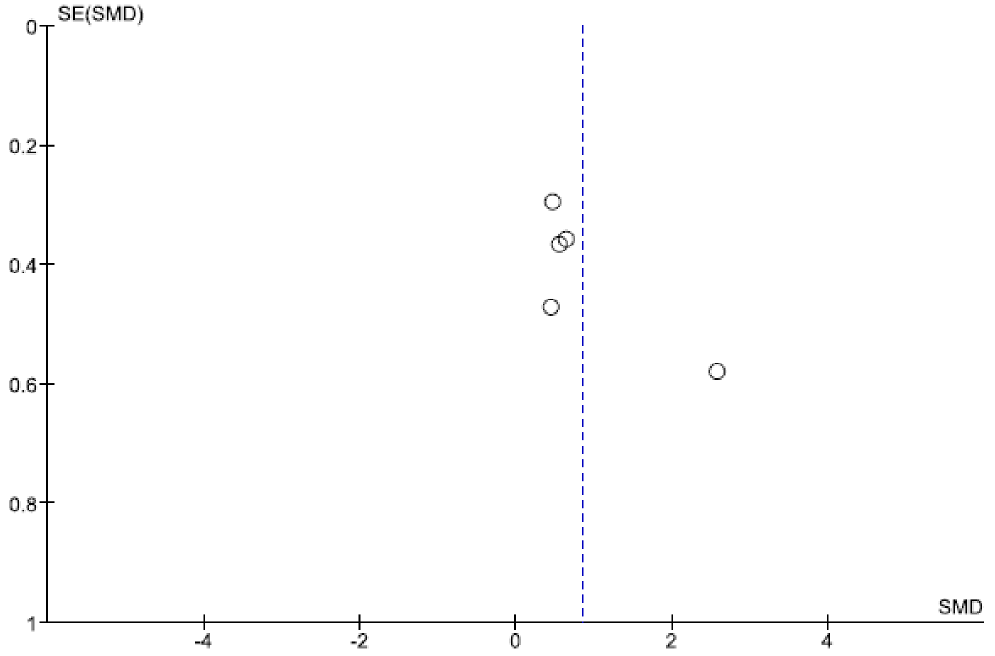

Figure S5d. Funnel plot of MCT on Walking speed.

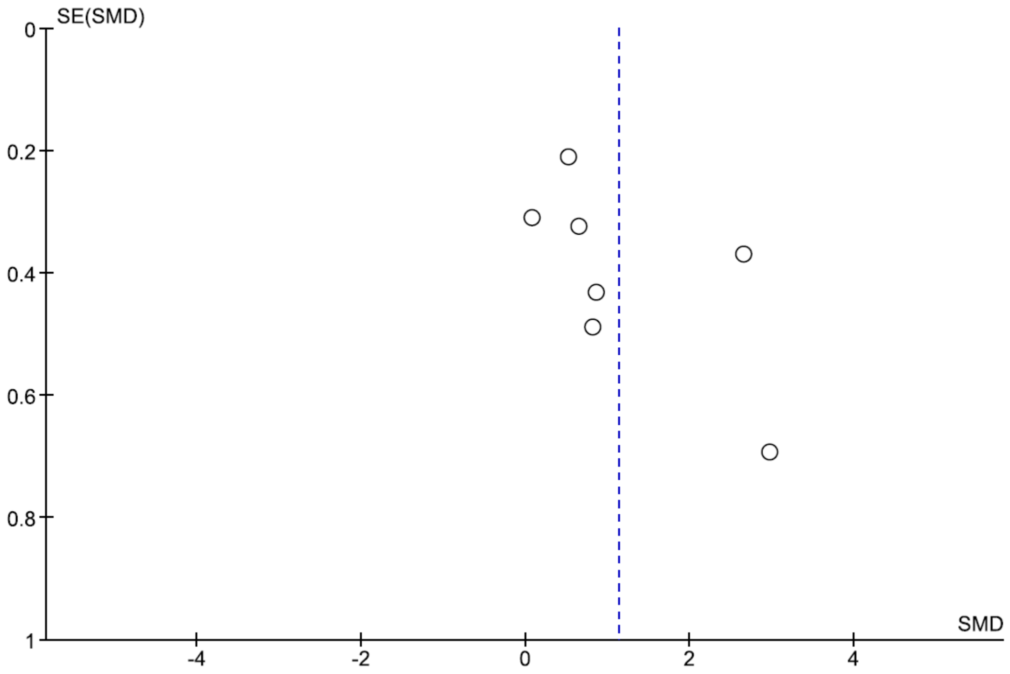

Figure S5e. Funnel plot of MCT on Lower limb strength.

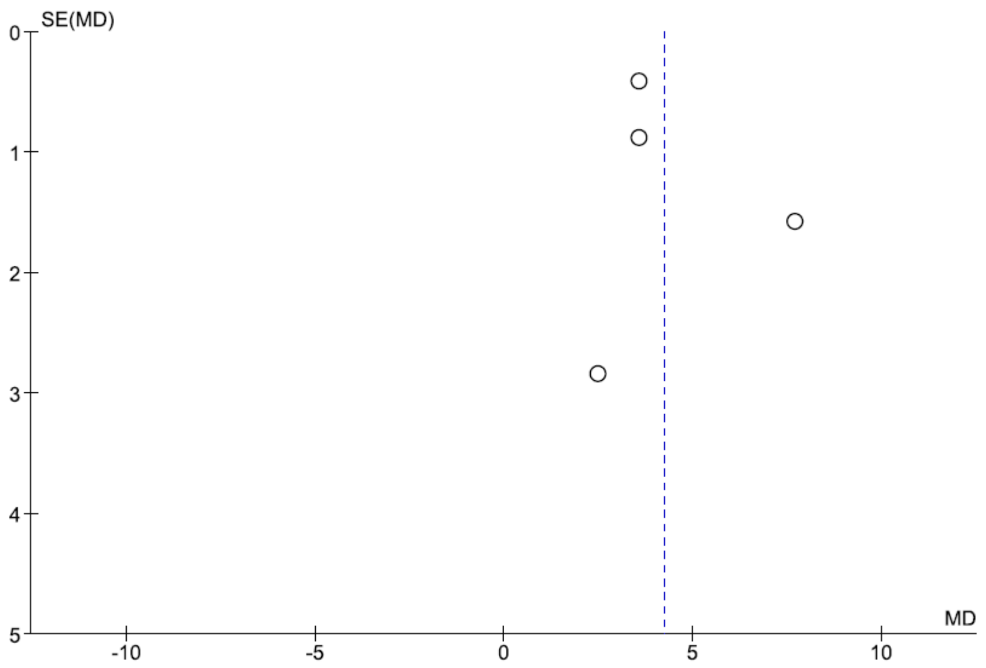

Figure S5f. Funnel plot of MCT on Upper limb strength.

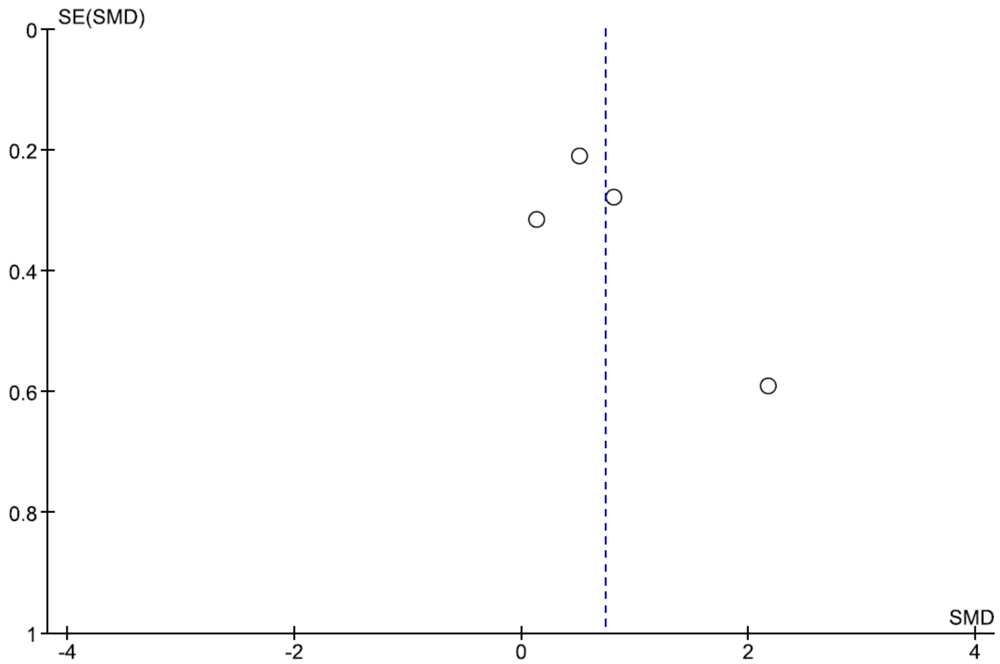

Figure S5g. Funnel plot of MCT against no training on Aerobic capacity.

Supplementary Appendix S6: Complete sensitivity analysis.

Table S6a. Sensitivity analysis for MCT on physical performance.

Study dropped out	SMD	95% CI	I^2
Ansai, 2016	0.83	[0.61, 1.04]	48%
Arrieta, 2018	0.79	[0.54, 1.03]	57%
Arrieta, 2019	0.75	[0.51, 1.00]	55%
Binder, 2002	0.80	[0.56, 1.04]	56%
Cadore, 2014	0.80	[0.56, 1.03]	56%
Carvalho, 2009	0.71	[0.51, 0.92]	42%
Makizako, 2012	0.80	[0.57, 1.04]	56%
Millor, 2014	0.78	[0.54, 1.01]	57%
Monteiro, 2019	0.57	[0.55, 1.03]	57%
Mulasso, 2015	0.78	[0.53, 1.02]	57%
Puggaard (2), 2003	0.56	[0.52, 0.90]	56%
Puggaard (3), 2003	0.82	[0.61, 1.04]	48%
Puggaard, 2003	0.76	[0.53, 0.99]	57%
Tarazona-Santabalbina, 2016	0.76	[0.52, 1.00]	56%
Toraman, 2004	0.74	[0.53, 0.95]	48%
None	0.78	[0.55, 1.00]	54%

SMD Standard Mean Difference; CI Confidence Interval; I^2 Heterogeneity Statistic

Table S6b. Sensitivity analysis for MCT on Short Physical Performance Battery (SPPB).

Study dropped out	MD	95% CI	I^2
Arrieta, 2018	2.68	[1.93, 3.42]	0%
Arrieta, 2019	2.28	[1.50, 3.06]	0%
Tarazona-Santabalbina, 2016	2.06	[1.72, 3.47]	13%
None	2.53	[1.89, 3.16]	0%

MD Mean Difference; CI Confidence Interval; I^2 Heterogeneity Statistic

Table S6c. Sensitivity analysis for MCT on Timed Up and Go Test (TUG).

Study dropped out	SMD	95% CI	I^2
Arrieta, 2018	1.03	[0.51, 1.55]	68%
Cadore, 2014	0.98	[0.46, 1.50]	76%
Carvalho, 2009	0.71	[0.31, 1.11]	55%
Monteiro, 2019	0.97	[0.42, 1.52]	77%
Mulasso, 2015	0.95	[0.33, 1.57]	77%
Toraman, 2004	0.76	[0.34, 1.18]	67%

None	0.90	[0.44, 1.35]	71%

SMD Standard Mean Difference; CI Confidence Interval; I^2 Heterogeneity Statistic

Table S6d. Sensitivity analysis for MCT on walking speed.

Study dropped out	SMD	95% CI	I^2
Arrieta, 2018	0.84	[0.24, 1.43]	66%
Cadore, 2014	0.56	[0.29, 0.83]	0%
Makizako, 2012	0.85	[0.30, 1.39]	65%
Puggaard (2), 2003	0.80	[0.26, 1.33]	66%
Puggaard (3), 2003	0.82	[0.29, 1.35]	66%
Puggaard, 2003	0.81	[0.31, 1.32]	66%
None	0.75	[0.32, 1.19]	58%

SMD Standard Mean Difference; CI Confidence Interval; I^2 Heterogeneity Statistic

Table S6e. Sensitivity analysis for MCT on lower limb strength.

Study dropped out	SMD	95% CI	I^2
Ansai, 2016	1.18	[0.54, 2.12]	86%
Arrieta, 2018	1.28	[0.38, 2.17]	87%

Cadore, 2014	1.19	[0.38, 2.01]	88%
Carvalho, 2009	0.79	[0.27, 1.30]	67%
Millor, 2014	1.19	[0.39, 2.00]	88%
Monteiro, 2019	1.24	[0.38, 2.10]	88%
Toraman, 2004	0.91	[0.23, 1.60]	84%
None	1.14	[0.43, 1.85]	86%

SMD Standard Mean Difference; CI Confidence Interval; I^2 Heterogeneity Statistic

Table S6f. Sensitivity analysis for MCT on upper limb strength.

Study dropped out	MD	95% CI	I^2
Arrieta, 2018	5.09	[1.35, 8.83]	80%
Carvalho, 2009	5.14	[1.34, 8.93]	76%
Monteiro, 2019	4.80	[2.59, 7.01]	80%
Toraman, 2004	3.58	[2.85, 4.31]	0%
None	4.53	[2.57, 6.50]	70%

MD Mean Difference; CI Confidence Interval; I^2 Heterogeneity Statistic

Table S6g. Sensitivity analysis for MCT on aerobic capacity.

Study dropped out	SMD	95% CI	I^2

Arrieta, 2018	0.91	[0.00, 1.83]	79%
Carvalho, 2009	0.77	[-0.06, 1.61]	78%
Monteiro, 2019	0.96	[0.27, 1.65]	72%
Toraman, 2004	0.51	[0.17, 0.84]	21%
None	0.74	[0.17, 1.30]	70%

SMD Standard Mean Difference; CI Confidence Interval; I^2 Heterogeneity Statistic

Artículo 7

Artículo 7	
Publicación	Effectiveness of different training modalities on Static Balance in Older Adults: A Systematic Review and Meta-Analysis
Autores	Noé Labata-Lezaun, Sergi Rodríguez-Rodríguez, Carlos López-de-Celis, Jacobo Rodríguez-Sanz, Max Canet-Vintró, Guillermo R Oviedo, Vanessa González Rueda, Albert Pérez-Bellmunt
Revista	Life
Quartil (2022)	Q2
Cita	Labata-Lezaun N, Rodríguez-Rodríguez S, López-de-Celis C, Rodríguez-Sanz J, Canet-Vintró M, R.-Oviedo G, et al. Effectiveness of Different Training Modalities on Static Balance in Older Adults: A Systematic Review and Meta-Analysis. Life [Internet]. 2023 May 16;13(5):1193. doi: 10.3390/life13051193. PMID: 37240838; PMCID: PMC10222379
Enlace web	https://pubmed.ncbi.nlm.nih.gov/37240838/
Participación	Primer autor
Contribución	Diseño del estudio, Realización de la revisión sistemática, Realización

del doctorando	del meta-análisis, Redacción del artículo

life

MDPI

Systematic Review

Effectiveness of Different Training Modalities on Static Balance in Older Adults: A Systematic Review and Meta-Analysis

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Abstract: (1) Background: aging is associated with functional changes such as balance, which plays a critical role in older adults. Physical exercise has been established as a factor capable of modulating these age-related alterations. (2) Methods: a meta-analysis of randomized clinical trials (RCTs) was conducted. The systematic search was performed in the PubMed/MEDLINE, Web of Science, the SPORTDiscus and Cochrane Library databases. Articles were included if participants were 65 years or older, healthy and performing resistance training, aerobic training, balance training or multicomponent training. Studies were excluded if there was a combination of training with other types of intervention. The protocol of this systematic review was published in the International Prospective Register of Systematic Reviews (PROSPERO) with the code CRD42021233252 (3) Results: the search strategy found a total of 1103 studies. After removing duplicates and the inclusion and exclusion criteria, eight articles were included in the meta-analysis, with a total of 335 healthy older adults analyzed. The results showed no significant differences between the intervention groups and the control groups after the exercise programs. (4) Conclusions: interventions based on different types of exercise improved static balance in elderly population, but without statistically significant difference in comparison with the control groups.

Keywords: balance; elderly people; older adults; training; exercise

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Effectiveness of different training modalities on Static Balance in Older Adults: A Systematic Review and Meta-Analysis.

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ABSTRACT

(1) Background: Aging is associated with functional changes like balance, which plays a critical role in older adults. Physical exercise has been established as a factor capable of modulating these age-related alterations. (2) Methods: A meta-analysis of randomized clinical trials (RCTs) was conducted. The systematic search was performed in the PubMed/MEDLINE, Web of Science, the SPORTDiscus and Cochrane Library databases. Articles were included if participants were 65 years or older, healthy and performing resistance training, aerobic training, balance training or multicomponent training. Studies were excluded if there was a combination of training with other types of intervention. The protocol of this systematic review was published in the International Prospective Register of Systematic Reviews (PROSPERO) with the code CRD42021233252 (3) Results: The search strategy found a total of 1103 studies. After removing duplicates and the inclusion and exclusion criteria, 8 articles were included in the meta-analysis, with a total of 335 healthy older adults analyzed. The results showed no significant differences between the intervention groups and the control groups after the exercise programs. (4) Conclusions: Interventions based on different types of exercise improved static balance in elderly population, but without statistically significant difference in comparison with the control groups.

KEYWORDS

balance, elderly people, older adults, training, exercise

1. Introduction

The global population of older adults is growing rapidly [1,2] and at the same time, life expectancy is lengthening. Aging is associated with biological, structural, metabolic and neuroendocrine changes that influence the musculoskeletal system, leading to a decline in physical abilities, cognition and brain structure [2-4]. Recent studies agree that with aging, and induced by decreases in strength, endurance and consequently balance, there is also an increased rate of falls, which increases rapidly at 75 years of age [1,5-9].

In everyday life, balance plays a critical role for older adults in avoiding and adapting to the external environment that threatens postural stability [6]. In sports practice the static balance could be fundamental [7]. Researchers highlight that postural sway during static standing increases with each decade of life in healthy adults aged 40 to 80 years [1]. They found that older adults rely on their visual field input to maintain balance. They further report that by the age of 70 years, the vestibular system shows a reduction, leading to less instability, and moreover there is a significant decrease in muscle strength leading to impaired balance [1,6,9].

In order to reduce these structural changes that accompany aging [3], physical exercise has been established as a factor capable of modulating age-related alterations, preventing muscle atrophy, maintaining cardiorespiratory capacity and cognitive function, improving metabolic activity and maintaining functionality [2,11]. Higher levels of physical exercise, such as multimodal training regimens that include strength, balance or general endurance tasks may reduce overall morbidity and improve quality of life [5,12-15].

It has been described in the scientific literature that there was no consensus regarding which of the critical elements of motor control needed to be trained to improve balance [8]. Currently, numerous multicomponent interventions (MCT) have been proposed to improve balance in older adults, such as strength training, aerobic exercise, or specific flexibility training [16]. In addition, the latest international consensus on exercise in older adults [17] described MCT programs as beneficial strategies to improve balance among other domains [17,18]. Other recent guidelines on fall prevention in older adults recommend in their guidelines exercise training modes that are highly challenging for balance, such as resistance training in addition to balance training [19].

In line with this, in recent years and research, several rehabilitation modalities with digital platforms, such as Exergames or Wii fit [20-22], based on physical-cognitive interaction through body movements, have emerged as promising approaches in the treatment of balance in older adults.

Although there is a large amount of scientific literature on therapeutic exercise and the benefits it brings, among other capacities, to balance in the elderly, there are many exercise modalities that have been proposed in recent years. The aim of this review is to evaluate, through an analysis of the scientific literature, which exercise modalities have the greatest benefits for balance in the elderly.

2. Materials and Methods

The present systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [23]. The protocol of this systematic review was previously published in the

International Prospective Register of Systematic Reviews (PROSPERO) with the code CRD42021233252.

2.1. Systematic literature search

First, a systematic literature search was conducted in the electronic search engines PubMed/MEDLINE and Web of Science, and in the SPORTDiscus and Cochrane Library databases until January 2023. Moreover, additional explorations were conducted weekly with automatic updates retrieved from the aforementioned databases. In addition, a manual search was conducted, and the bibliography of other similar systematic reviews was checked in order to find potential studies. The complete search strategies are available on the Supplementary Appendix S1.

In order to develop an accurate search strategy, the PICOS strategy was used [24]. Four domains were included. Population: healthy older adults; Intervention: resistance training (RT), aerobic training (AT), balance training (BT) or multicomponent training (MCT), including at least 3 training modalities; Comparison: no training; Outcome: static balance; Study design: randomized control trials (RCTs). Filters proposed by the Cochrane Collaboration for RCTs were also combined with the search strategy [25].

2.2. Selection criteria

Inclusion criteria: randomized controlled trial study design, older adults aged >65, considered as healthy participants, intervention group with a RT, AT, BT or MCT, comparison group with no training, static balance as outcome, and English language. Exclusion criteria: combination of training with other types of intervention.

2.3. Screening, selection and data extraction process

Once the systematic search was conducted, all titles, abstracts, and full text were independently screened by two researchers (JRS and MCV) for potential inclusion. A third researcher (NLL) was consulted for a decision in case of discrepancy. Rayyan software (https://rayyan.qcri.org) was used in order to perform the screening process [26]. The following data was extracted from every included study: author's last name, year of publication, sample size, sample characteristics (number of participants in each group, age and gender distribution), characteristics of the training (duration of the program, frequency, volume, intensity, and exercise selection), control group characteristics, outcomes, main results. The data was extracted independently by two reviewers (NLL and CLdC).

2.4. Methodological quality and risk of bias

Methodological quality and Risk of bias of the included studies were independently evaluated by two authors (APB and NLL) using the Physiotherapy Evidence Database (PEDro) scale [27], and the Cochrane Risk of Bias (RoB2) assessment tool [28] .

The PEDro scale was especially designed to assess the methodological quality of the Physiotherapy studies. It was developed to assess 3 domains (external validity, internal validity and statistical reporting), and included the following 11 items: 1) eligibility criteria and source 2) random allocation, 3) concealed allocation, 4) baseline comparability, 5) blinding of participants, 6) blinding of therapists, 7) blinding of assessors, 8) adequate follow-up (>85%), 9) intention-to-treat analysis, 10) between-group statistical comparisons, 11) point measures and variability data. All items achieved are scored 1, and the total PEDro score is calculated by adding items 2 to 11, with a maximum score of 10. PEDro score <4 is considered “poor”; from 4 to 5 “fair”; from 6 to 8 “good” and 9 to 10 “excellent” [27].

RoB2 is a widely accepted tool in the biomedical scientific field, proposed by Cochrane Collaboration [28] , to evaluate the potential risk of bias of a RCT. It is divided in six domains, involving the following 8 items: randomization sequence generation, allocation concealment, blinding participants, blinding therapist, blinding outcome assessor, incomplete outcome data, source of funding bias/selecting outcome reporting and other bias. Each item is categorized in 3 scores: low (green), unclear (yellow) or high (red) risk of bias.

2.5. Data synthesis and analysis

The Review Manager 5 software (Cochrane Collaboration, Oxford, UK) was used to perform the statistical analysis. As all outcomes were continuous, sample size, post-intervention means, and standard deviation (SD) were extracted. Corresponding authors were contacted by e-mail if any data not reported in the paper was required.

The mean difference (MD) was chosen as effect size, when studies used the same tool of measure. The standard mean difference (SMD) was chosen as effect size when studies used different tools of measure. Effect size was expressed with a 95% confidence interval (95%CI). The inverse of the variance (IV) statistical test was used for the quantitative analysis, using a random-effects model to determine the overall effect size, as the number of included studies was considered small [29]. eStatistical significance was set at $p<0.05$.

The heterogeneity was evaluated by using I^2 statistics, and it was classified as low ($I^2 \leq 25\%$), moderate ($25<I^2<50\%$), or high ($I^2 \geq 50\%$) [30] When high heterogeneity (I^2

>50%) was found, a heterogeneity analysis using subgroups was performed. Finally, visual inspection of the funnel plots was performed to assess potential publication biases if the number of the included studies was more than 10 [31].

3. Results

3.1. Study selection

The search strategy found 1103 studies (Cochrane Library: 258; PubMed: 338; Web of Science: 363; SPORTDiscus: 144). After removing duplicates, a total of 747 studies were initially considered to be included. Seven hundred and four studies were excluded after screening the titles and abstracts for not meeting the inclusion criteria. After assessing the full text, 9 studies met the inclusion criteria for the qualitative analysis, and 34 articles were excluded. One study dropped out from the meta-analysis for not presenting the required data, after contacting the corresponding author. Finally, 8 articles were included in the quantitative synthesis, 3 for the RT intervention [32–34], 3 for the BT intervention [32,32,35], and 2 for the MCT intervention [36,37]. *Figure 1* presents the PRISMA flow diagram [23].

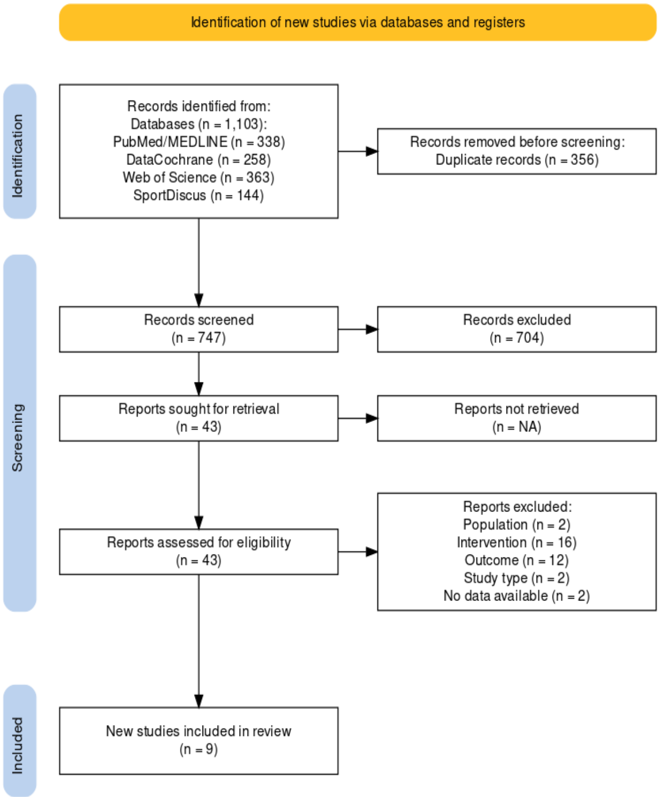

Figure 1: PRISMA 2020 Flow Diagram

3.2. Study Characteristics

Table 1 summarizes the sample characteristics of the nine included articles. A total of 335 elderly individuals were included in this systematic review. Although most of the articles analyzed both men and women, the distribution was greater for women. The sample size varied between 12 [38] and 55 [33] individuals, with an average age In terms of the duration of the interventions, the training programs varied from 3 [38] to 48 weeks [37], with a frequency of 2 to 3 sessions per week. As for the control group, seven studies included a non-training group, one included educational sessions [33] and another one included a walking activity [34]. Only the studies by Cadore et al. [40] and Forte et al. [41] included a resistance-training comparison group. Finally, regarding the study variables static balance was assessed with the One-Legged Stance test in five studies, with the Berg Balance Scale in two studies [35,38], with the Romberg test in one study [32], and with the Short Physical Performance Battery (balance test) in another study [36].

Table 1. Study characteristics

Study	N (IG /CG)	Age (±SD)	Gender (F/M)	Modality	Variable
Wolfson, 1996	55 (28/27)	80	32/23	BT	OLS-CE
Wolfson, 1996	55 (28/27)	80	34/21	RT	OLS-CE
Earles, 2001	40 (18/22)	78 ± 5	26/14	RT	OLS
Kronhed, 2001	30 (15/15)	73 ± 2	16/14	BT	Romberg
Mian, 2007	38 (25/13)	73 ± 3.4	19/19	MCT	OLS
Kobayashi, 2012	24 (17/7)	67.5 ± 5.23	14/10	RT	OLS-CE
Bieryla, 2013	12 (6/6)	81.5 ± 5.5	10/2	BT	BBS
Sato, 2015	58 (29/28)	69.25 ± 5.41	43/14	BT	BBS
Marques, 2017	47 (24/23)	69	47/0	RT	OLS
Marques, 2017	48 (24/24)	69	48/0	AT	OLS
Adcock, 2020	31 (15/16)	73.9 ± 6.4	16/15	MCT	SPPB Balance

IG: intervention group; CG: control group; BT: balance training; RT: resistance training; MCT: multicomponent training; AT: aerobic training; M: male; F: Female; SD: standard deviation; OLS: one-legged stance test; CE: closed eyes; BBS: Berg balance scale; SPPB: short physical performance battery

3.3. Methodological quality

The average score for the PEDro scale was 5/10, which is considered as a “fair” methodological quality across the studies included in the systematic review. The main recurrent methodological problems were blinding of participants and therapists (0/9 studies); and blinding of assessors, concealed allocation, and intention-to-treat analysis (2/9 studies) (*Table 2*) [27].

Table 2. PEDro Scale

Study	1	2	3	4	5	6	7	8	9	10	11	Total
Wolfson 1996	1	1	0	1	0	0	1	1	0	1	1	6
Earles 2001	1	1	0	1	0	0	0	1	0	1	1	5
Kronhed 2001	1	1	1	1	0	0	0	0	1	1	1	6
Mian 2007	1	1	0	1	0	0	0	0	0	1	1	4
Kobayashi 2012	1	1	0	1	0	0	0	1	0	1	1	5
Bieryla 2013	1	1	0	1	0	0	0	0	0	0	1	3
Sato 2015	0	1	0	1	0	0	0	1	0	1	1	5
Marques 2017	1	1	0	1	0	0	1	0	1	1	1	6
Adcock 2020	1	1	1	1	0	0	0	0	0	1	1	5
Average												**5***

1: Inclusion/Exclusion Criteria; 2: Random Allocation of Participants; 3: Concealed Allocation; 4: Similarity Between Groups at Baseline; 5: Participant Blinding; 6: Therapist Blinding; 7: Assessor Blinding; 8: Fewer than 15% Dropouts; 9: Intention- to-Treat Analysis; 10: Between- Group Statistical Comparisons; 11: Point Measures and Variability Data. * Item 1 is not used to calculate the PEDro score.

3.4. Risk of bias

Figure 2 shows the RoB 2 tool summary and graph. Again, a high risk of bias was found in terms of performance bias (9/9), selection bias (7/9) and detection bias (7/9).

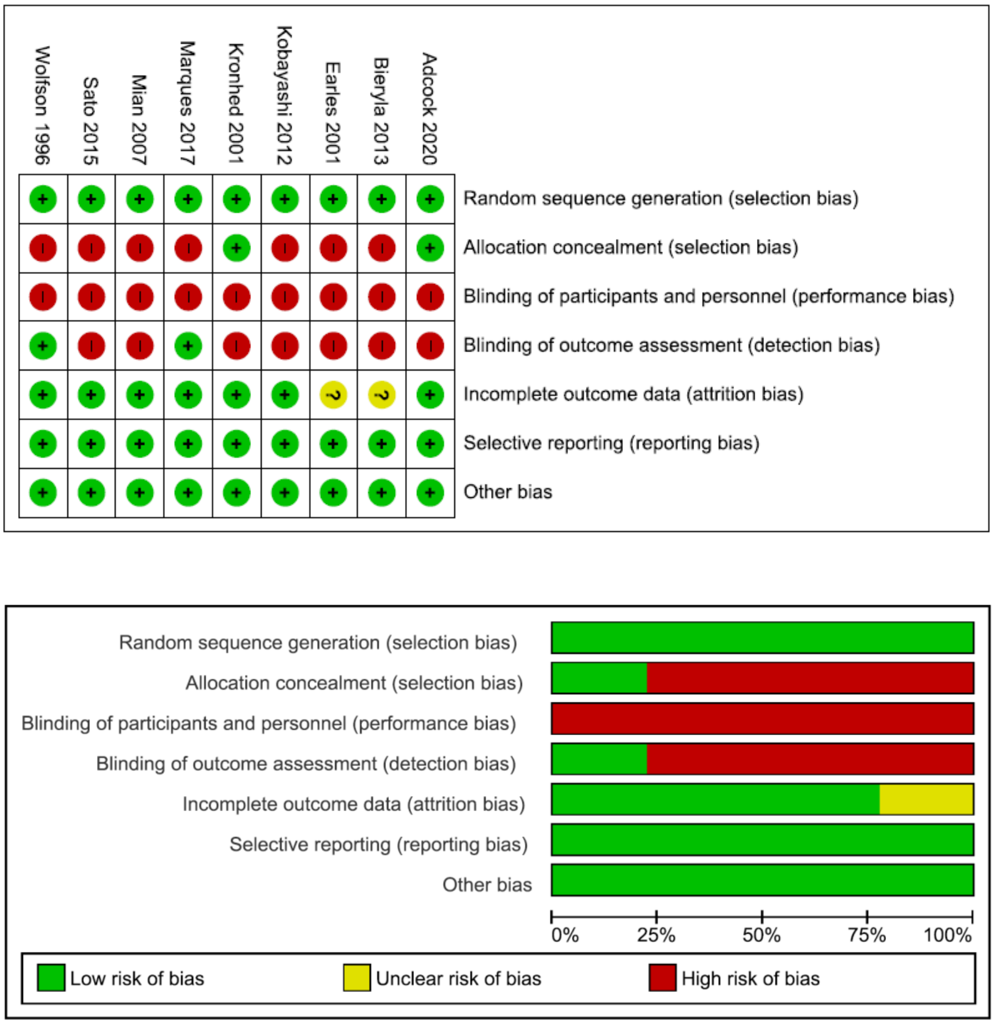

Figure 2: Risk of bias graph and summary

3.5. Effectiveness of interventions

3.5.1 Resistance Training

Four articles reported results about resistance training [33,34,39,42]. The study conducted by Earles et al. [34] focused on speed-based strength training. Among their results, they found improvements in strength, but not in functional capacity, which included the static balance variable. In the work carried out by Kobayashi et al. [39], they found improvements in static balance after performing a specific strength training protocol with respect to the control group. In the study carried out by Marques et al. [19], they also found improvements in static balance with respect to the control group. Finally, in the study conducted by Wolfson et al. [33], non-significant improvements in static equilibrium were found. For methodological reasons when reflecting the results, and after contacting the corresponding author, the data obtained in the study of Marques et al. could not be included in the quantitative analysis, so 3 studies were included, with a total of 119 participants. *Figure 3* shows the comparison between RT and the control group. Analysis shows an overall SMD of 1.99 [95%CI -0.97; 4.95] and an overall effect of Z=1.32 (p=0.19). The heterogeneity was considered moderate (I^2=49%).

	Resistance Training			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Earles 2001	11.2	2.5	18	8.5	8.7	22	31.5%	2.70 [-1.11, 6.51]
Kobayashi 2012	22	17.7	17	13.1	5.4	7	8.7%	8.90 [-0.42, 18.22]
Wolfson 1996	10	2.5	28	9.4	2	27	59.7%	0.60 [-0.59, 1.79]
Total (95% CI)			**63**			**56**	**100.0%**	**1.99 [-0.97, 4.95]**

Heterogeneity: Tau² = 3.44; Chi² = 3.93, df = 2 (P = 0.14); I² = 49%
Test for overall effect: Z = 1.32 (P = 0.19)

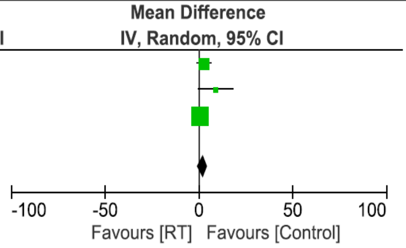

Figure 3: Effectiveness of resistance training on static balance

3.5.2. Aerobic Training

In reference to aerobic training, only one article was included in the qualitative analysis. The study carried out by Marques et al. [42] found improvements in static balance with respect to the control group after an aerobic training program with an intensity from 50% to 85% of the reserve heart rate.

3.5.3. Balance Training

Four studies [32,33,35,38] evaluated the effectiveness of balance training in improving static balance. Only studies conducted by Bieryla et al. and Wolfson et al. reported significant improvements. For methodological issues when reporting the results, and after contacting the corresponding author, the data obtained in the study of Bieryla et al. could not be included in the quantitative analysis, so 3 studies were included, with a total of 119 participants. *Figure 4* shows the comparison between BT and the control group. Analysis shows an overall SMD of 1.24 [95%CI -0.58; 3.06], and an overall effect of Z=1.33 (p=0.18). The heterogeneity was high (I^2=95%).

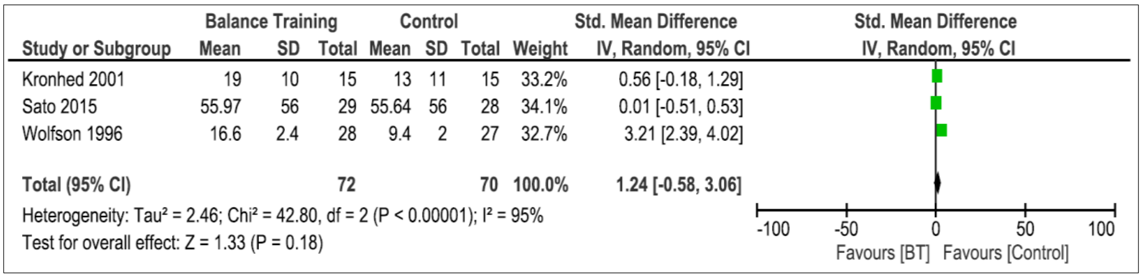

Figure 4: Effectiveness of balance training on static balance

3.5.4. Multicomponent Training

Two studies [35,36] evaluated the effectiveness of MCT in improving static balance, without obtaining differences with respect to the control group in any of them. Sixty-nine participants were included in the meta-analysis. *Figure 5* shows the comparison between MCT and the control group. Analysis shows an overall SMD of 0.33 [95%CI -0.31; 0.97], and an overall effect of Z=1.01 (p=0.31). The heterogeneity was moderate (I^2=41%).

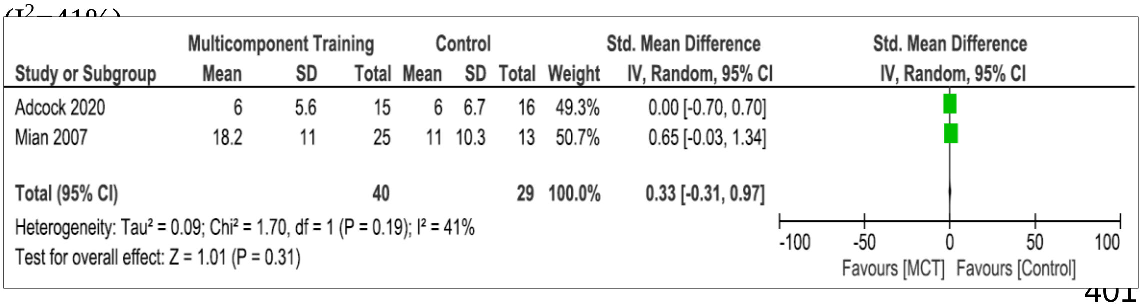

Figure 5: Effectiveness of multicomponent training on static balance

4. Discussion

The present study aims to analyze the effects of different types of training such as aerobic, resistance, multicomponent and balance training on static balance in the healthy elderly population. This systematic review summarizes the findings from a total of 8 studies and includes a total of 335 participants. Having described the results in the previous section, our review shows no significant statistical differences between any of the training modalities mentioned and their respective CGs, in terms of improvements in static balance.

4.1. Resistance training

It is important to note that the heterogeneity between studies was moderate for resistance training (I2 = 49%). This could be explained by the difference in the years of publication of the studies analyzed by Earles et al., Kobayashi et al. and Wolfson et al., the difference in sampling and that the study by (Wolfson et al.) adds balance training to their intervention.

The results of the present study are in agreement with those of previous studies (Knerl C et al.) [42] that found no significant improvement in balance after a resistance exercise programme compared to CG. Furthermore, Motalebi SA et al. [43] found significant improvements in lower limb strength and dynamic balance when applying a resistance programme, but static balance values measured with Tandem Stand (TS) and One Leg Stand (OLS) showed no improvement after 12 weeks. Schlicht et al. [44] also found no significant improvement in static balance after 8 weeks of intensive lower limb resistance training. This could be explained by the fact that several studies (Kobayashi et al., Schlicht et al. and Knerl C et al.) present an intervention time shorter than 12 weeks, which is the minimum recommended time by Fragala MS et al. [44]. Still, more research should be done to analyze the effects of resistance training with durations shorter than 12 weeks.

4.2. Multi-component training

Multicomponent training has considerable adherence among older populations, being a modality that has the characteristic of encompassing different abilities [46]. Previous trials have highlighted the potential benefits of a multicomponent exercise programme (resistance, aerobic endurance, flexibility and balance exercises) of long duration (i.e. 6 months or more) on functional capacity in older populations [16].

After analyzing the results, we highlight that the heterogeneity between studies (Adcock et al. and Mian et al.) was moderate for multicomponent training (I2 = 41%). This could be due to the difference in the year of publication between the studies, the type of intervention and the duration of the sessions.

In our review, no significant statistical differences in terms of improvement of physical abilities such as static balance were found between the intervention group and the CG after an MCT programme. In controversy with our results, another study by Sadjapong

U et al. [47], where a multicomponent exercise programme was performed in older adults, found significant improvements in balance (BERG test and TUG test) compared to baseline ($p<0.001$), compared to the CG. The study by Casas HA et al. [16], found significant differences after a multicomponent programme in older adults in Spain, 0.86 points in SPPB score (95 % CI 0.32, 1.41; $p<0.01$) after 1 month and 1.40 points (95 % CI 0.82, 1.98; $p<0.001$) after 3 months.

Previous trials [48] have highlighted the potential benefits of an MCT programme (resistance, endurance, flexibility and balance exercises) on functional capacity in older populations following exercise interventions of longer duration, i.e. 6 months or more. This could explain why there is no significant change in the results of the study by Adcock et al., as in their study, the intervention was performed without professional supervision from home and for a duration of less than 6 weeks. In the study by Mian et al., part of the intervention was also conducted from home, unlike the study by Sadjapong U et al. where the 12-week multicomponent exercise intervention was guided and supervised by therapists. Recent studies [47] concur on the problems of older adults in finding strategies to increase their adherence and motivation to home-based exercise programs.

4.3. Balance training

Balance is defined as the ability to maintain an upright posture during static and dynamic tasks, and requires complex interactions between central factors such as vision, somatosensation, vestibular sensation, motor skills and musculature [42]. Intervention programs that incorporate balance-challenging exercises have been shown to reduce the risk of falls among older adults [22].

With regard to the characteristics of the different interventions, once the results have been analyzed, we have seen that there is heterogeneity of over 40% in all the variables studied, with the studies on balance training being those with the highest heterogeneity (I2 = 93%). This could be due to the fact that the 3 studies were published in very different years, the difference in sample size and that the study by Wolfson et al. also performed resistance training in addition to balance training.

In the study by Lopez JC et al. [49], they observed that both groups improved unipodal and bipodal balance with both eyes open and closed after the intervention on unstable platforms; both differences were statistically significant ($p<0.01$). This study is in agreement with the balance improvements reported in our review study (Wolfson L et al.), who performed balance and strength interventions on stable surfaces, including Ti-Chi methods. Javadpour S et al. and Sinaei E et al. [50,51], showed significant improvements in static balance and dynamic balance in the single-task (ST) and dual-task (DT) training groups after 6 weeks in Javadpour S study and 4 weeks of training in Sinaei E study, while no statistically significant changes were shown in the control group.

In our review, no statistically significant changes were observed between the balance exercise-based intervention and CG groups. Only Wolfson et al showed significant improvements. This could be due to the fact that in the Wolfson et al study, in addition to balance training, resistance training was also performed. Two studies (Sato K et al. and Kronhed ACG et al.) did not show significant results compared to the control group in comparison to the other studies mentioned [49-51]. This could be explained by the fact that the studies by Sato K et al. and Kronhed ACG et al. did not use dual task exercises in their interventions and by the fact that the intervention by Sato K et al. used

Exergames in older adults, as it has been described [20] that research on persuasion in technology has not yet focused on older adults, which may not motivate or hinder their rehabilitation if done through Exergames.

4.4. Aerobic training

One of the reported benefits of aerobic activity is the improvement of balance and the reduction of the risk of falls and subsequent injuries caused by such an accident [52].

The study by Marques et al. found that aerobic exercise has a similar effect to that produced by strength training on static balance in older women aged 61-83 years, with respect to CG after an aerobic training programme, at an intensity of 50% to 85% of heart rate reserve. Spagnuolo et al. [53] and colleagues also found contrasting results with a strong correlation between the performance achieved on the incremental out-and-back walking test (ISWT) and the Berg balance scale in older adults, but aged 40-84 years (r = 0.61). The above results are consistent with the following study [54], a programme that included dancing as an aerobic exercise for 1 hour, 3 times per week, for 12 weeks, observed significant changes in static balance in women over 70 years of age. In addition, Vidarte-Claros JA et al. [55] showed changes in balance in older people who performed the exercise programme for 12 weeks, with similar effects on reducing the risk of falls.

In controversy, Hayashi D et al. [56], found no correlation between postural balance and exercise capacity in the whole group of older adults. This could be due to the fact that part of their sample were physically independent older adults according to the classification proposed by the Functional Status Spirduso.

4.5. Limitations of the study

Regarding the limitations of this study, it is important to comment on the heterogeneity of the results of each study, as well as the intrinsic characteristics of the studies. It can be stated that the lack of homogeneity of the different studies, due to, among other factors, differences in year of publication, sample size and type of intervention, may have contributed to show statistically non-significant results.

Furthermore, we are aware that the number of studies added to the review is small and that in one of the studies, the author did not provide us with the data. Regarding the characteristics of the sample, we note that although all the studies analyzed older adults, in some of the studies the physical abilities of the participants varied, which may have increased the heterogeneity.

5. Conclusions

In view of our results, we can conclude that different modalities of training improve functional capacities such as strength, balance and the risk of falls in healthy elderly people, but the difference on static balance is not significant when comparing with the control groups. These results make us see the need to continue studying different modalities of interventions that can significantly improve balance in older adults. Further research should be done to analyze the effects of these interventions in the long terms and with larger sample sizes. The present study focuses on the static analysis of equilibrium, the results may differ if the dynamic equilibrium is analyzed.

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Conflicts of Interest: The authors declare no conflict of interest.

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Artículo 8

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Effectiveness of a Multicomponent Training Program on Physical Performance and Muscle Quality in Older Adults: A Quasi-Experimental Study

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Abstract: Aging is associated with a decrease in functional capacity, manifested by a loss of strength, physical performance and muscle quality. Multicomponent training (MCT), characterized by the combination of at least three types of training, could be a good strategy to counteract these changes. To date there are no studies evaluating the effectiveness of MCT in improving both physical performance and muscle quality simultaneously. The aim of this study is to evaluate the changes produced by an MCT program on both physical performance and muscle quality in a population of healthy older adults. Sixteen healthy older adults were recruited to perform a 15-session multicomponent training intervention. Physical performance was assessed by different functional tests, and muscle quality was assessed by tensiomyography and myotonometry. The main results of this study show some improvement in functional tests, but not in muscle quality parameters, except for vastus lateralis stiffness. MCT is able to generate improvements in the physical performance of older adults, but these improvements are not reflected in muscle quality parameters measured by tensiomyography and myotonometry.

Keywords: elderly; muscle quality; physical functional performance; multicomponent training

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Effectiveness of a Multicomponent Training Program on Physical Performance and Muscle Quality in Older Adults: A Quasi-Experimental Study

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ABSTRACT

Aging is associated with a decrease in functional capacity, manifested by a loss of strength, physical performance and muscle quality. Multicomponent training (MCT), characterized by the combination of at least three types of training, could be a good strategy to counteract these changes. To date there are no studies evaluating the effectiveness of MCT in improving both physical performance and muscle quality simultaneously. The aim of this study is to evaluate the changes produced by an MCT program on both physical performance and muscle quality in a population of healthy older adults. Sixteen healthy older adults were recruited to perform a 15-session multicomponent training intervention. Physical performance was assessed by different functional tests, and muscle quality was assessed by tensiomyography and myotonometry. The main results of this study show some improvement in functional tests, but not in muscle quality parameters, except for vastus lateralis stiffness. MCT is able to generate improvements in the physical performance of older adults, but these improvements are not reflected in muscle quality parameters measured by tensiomyography and myotonometry.

KEYWORDS

elderly; muscle quality; physical functional performance; multicomponent training

1. Introduction

During the last decades, the increase in life expectancy has been causing a general aging of the population. In Europe, approximately 20% of the population is over 65 years of age [1]. In addition, aging involves structural [2], metabolic [3], and neuroendocrine changes [4] that influence the musculoskeletal system and ultimately lead to a decrease in physical performance [2]. The World Health Organization (WHO) defined healthy aging as "the process of developing and maintaining functional capacity that enables well-being in old age" [5]. In this sense, emphasis is placed on the preservation of physical performance, which ensures the person's independence.

For their part, international organizations such as the European Working Group on Sarcopenia in Older People (EWGSOP), emphasize i the importance of the assessment of both strength and physical performance in the diagnosis of sarcopenia in their latest consensus [6]. Moreover, the organization highlights the relevance of assessing not only the quantity, but also the muscle quality (micro and macroscopic aspects of muscle architecture and composition); and admits the current challenge of finding reliable tools capable of assessing it [6]. In recent years, several tools for assessing muscle quality, such as tensiomyography and myotonometry, have been developed. Tensiomyography is a valid and reliable method of assessing muscle quality [7,8]. It assesses stiffness by measuring the radial displacement of the transverse fibers of the muscle belly as a function of the time in which the contraction occurs. Myotonometry is another valid and reliable method of assessing muscle function used to evaluate the viscoelastic properties of tissues [9–12]. Although both tools are used to assess the intrinsic properties of tissues, their results cannot be exchanged one for the other [13].

Regarding the different strategies to ensure "healthy aging”, physical exercise has been shown to be effective in modulating aging-related changes, preventing muscle atrophy, maintaining cardiorespiratory fitness and maintaining functional independ-ence [14–16]. In particular, multicomponent training (MCT) characterized by the com-bination of at least three types of training such as resistance, aerobic, balance, and/or flexibility training has shown to be effective in improving the physical performance in large sample randomized controlled clinical trials [17] and meta-analyses [18]. In fact, the latest international consensus on exercise in the older adults promotes the imple-mentation of MCT programs as one of the best strategies for improving strength, bal-ance and gait, as well as reducing falls [19].

Although the effectiveness of MCT in improving physical performance has been extensively studied, to date there are no studies evaluating the effectiveness of MCT in improving both physical performance and muscle quality. Thus, the aim of this study is to evaluate the changes produced by an MCT program on both physical performance and muscle quality in a population of healthy older adults.

2. Materials and Methods

2.1. Study Design

This is a quasi-experimental study. The study protocol was registered in Clinical-Trials.gov with the code NCT05286723.

2.2. Participants

Twenty participants were recruited according to their availability to participate through the Associació de Gent Gran Casal Anna Murià (Terrassa). Four participants were finally unable to take part in the intervention, two for COVID reasons, one for having suffered a fall prior to the measurements, and one for musculoskeletal issues.

The study was approved by the Research Ethics Committee of the Universitat Internacional de Catalunya (CBAS-2021-08). All participants signed a written informed consent document before enrolling in the study. Data protection laws were respected according to the Helsinki declaration.

Prior to measurements, the attending geriatricians reviewed the absolute and rel-ative contraindications to participate in the intervention.

The inclusion criteria were (a) persons over 65 years of age, and (b) able to carry out a therapeutic exercise program.

Exclusion criteria were (a) the inability to stand or ambulate in an unassisted manner, (b) previous bone fracture in the last 6 months, (c) uncontrolled symptomatic cardiovascular or respiratory disease, (d) uncontrolled hypertension, (e) current cancer under treatment, and (f) inability to understand the information provided by the researchers.

An attendance percentage of 60% of the training sessions was established in order to be included in the statistical analysis. Drop-out was considered only when the pre-intervention assessment was completed.

2.3. Procedure

Once the subjects were contacted, it was confirmed that they met the inclusion/exclusion criteria and they were scheduled for the evaluation. Pre-intervention measurements took place in October 2021. First, anthropometric data were recorded and questionnaires were handed out. Subsequently, muscle quality and physical performance were assessed. At the end of the intervention period, post-intervention measurements were taken in December 2021 following the same structure used previously.

2.4. Intervention

The intervention began in November 2021, and took place in the Casal Gent Gran Anna Murià. The intervention consisted of 15 sessions of multicomponent training over a period of 2 months, with a training frequency of two sessions per week. The duration of the sessions was 1 hour. The intervention was carried out by a physiotherapist and a physical trainer. During the sessions, a 15-minute warm-up was performed, which included joint mobility exercises, gait work, active stretching, and balance and coordination exercises. The main part of the training consisted of 30 minutes of strength training, in which pull, push, squat and deadlift patterns were worked using dumbbells of different weights to adjust the workload. The difficulty of the exercises was adapted for each of the participants. Three sets of 8–12 repetitions were performed for each movement, increasing the load to ensure a moderate-high intensity of 7–8 in rate of perceived exertion (RPE). A 90-second rest was taken between each set. The session ended with 15 minutes of unmonitored aerobic exercise, including collaborative games or going up and down stairs. Adherence to the programme was documented in a daily register, and phone calls were made in case the person did not attend the training session.

2.5. Variables

The variables measured can be grouped into physical performance variables and muscle quality variables. To assess physical performance, the following tests were used: Short Physical Performance Battery (SPPB), walking test, Five Times Sit-to-Stand Test (5XSST), Timed Up and Go test (TUG), and handgrip strength. The muscle quality parameters assessed were contraction time and maximal radial displacement, measured by tensiomyography, and stiffness as measured by myotonometry.

2.5.1. Short Physical Performance Battery (SPPB)

This is a test battery consisting of three tests. It consists of a balance test, a four meters walking speed test and a test of sitting down and getting up from the chair five times. Each result has a value of 0–4 points which is summed to obtain an overall score of 0–12 points. Test-retest reliability has been shown to be good to excellent (ICC 0.83–0.92), and the inter-rater reliability (ICC 0.91) among acutely admitted older adults was shown to be excellent as well [2].

2.5.2. Meters Walking Test (4WT)

This is a functional test that reflects the average speed in which the subject takes to walk 4 meters. Although it is included in the SPPB battery, its score has a value by itself. The test was performed twice and the one with the shorter time was chosen. Its relia-bility has been previously studied (ICC = 0.96, 95%CI = 0.94–0.98; SEM = 0.01) [20].

2.5.3. Five Times Sit-to-Stand Test (5XSST)

This reflects the time in seconds it takes the person to sit down and stand up five times from a chair, without the help of the arms. Although it is included in the SPPB battery, its score has a value on its own. The test was performed twice and the one with the shorter time was chosen [2].

2.5.4. Timed Up and Go Test (TUG)

This is a functional test that reflects the time in seconds that it takes the person to get up from the chair, with the help of the arms, walk 3 meters, turn around an obstacle, return to the chair and sit down again [6]. The test was performed twice and the one with the shorter time was chosen. Its reliability has been studied previously (ICC = 0.98, 95%CI = 0.93–1.00; SEM = 0.7) [2].

2.5.5. Handgrip Strength

This is a test that reflects the maximal grip strength in kilograms (Kg) using a hand dynamometer [21,22]. The device used was the Jamar® dynamometer. In order to perform the measurements, the subject was placed in a seated position with the arms supported ensuring 90° elbow flexion with the wrists in a neutral position. Both the dominant and non-dominant arms were measured. Three measurements were taken for each hand, with a one-minute rest between measurements. The mean between the three measurements of each hand was calculated and the hand that obtained the best results was chosen. The validity and reliability of this device has been evaluated in previous studies (ICC = 0.98) [2,23]

2.5.6. Maximal Radial Displacement (Dm)

Concentric muscle contraction is produced by the sliding of the actin myofilaments over the myosin myofilaments in the sarcomeres. As a result, a decrease in their lon-gitudinal section is generated, which in turn generates an increase in the cross-sectional area of the muscle. This increase in cross-section is visualized by a displacement in a radial direction, i.e., perpendicular to the muscle belly. Maximal radial displacement of the muscle in millimeters is measured with tensiomyography under an involuntary contraction by electrostimulation [13]. In the present study, the rectus anterior quadriceps and vastus lateralis muscles were measured. To perform the measurement, the patient must be placed in a muscle relaxation position, generally in the decubitus position. Two electrodes (TMG electrodes, TMG-BMC d.o.o., Ljubljana, Slovenia) are placed on the most prominent part of the chosen muscle belly at a distance of 5 centimeters between electrodes. In addition, the Dc-Dc Trans-Tek® transducer (GK40, Panoptik d.o.o., Ljubljana, Slovenia) is placed perpendicularly. Through an electrostimulator de-vice (TMG- BMCd.o.o., Ljubljana, Slovenia) connected to the electrodes, an involuntary contraction of the muscle is generated, causing radial displacement of the sensor and generating a time-displacement curve. The amplitude is progressively increased from 20 to 100 mA by increments of 20 mA until no further increase in Dm is recorded or the maximum point of the stimulator is reached (i.e., 110 mA). Ten seconds of rest was performed between stimuli to minimize the effects of fatigue and post-activation po-tentiation [24].

2.5.7. Contraction Time (Tc)

This reflects the time measured in milliseconds that the muscle takes to reach 10 to 90% of the maximal radial displacement (Dm) [24]. In the present study, the rectus an-terior quadriceps and vastus lateralis muscles were measured using tensiomyography.

2.5.8. Stiffness

It is a variable determined by the ratio between the force produced by the me-chanical impulse and the depth of tissue deformation using myotonometry. Its unit of measurement is newtons per meter ($N \cdot m^{-1}$). In the present study, the rectus anterior quadriceps and vastus lateralis muscles were measured. To perform the measurement, the patient must be in a muscle relaxation position. The sensor of the device is then placed perpendicular to the most prominent part of the chosen muscle belly (only su-perficial musculature can be assessed). From this position, a small pressure is exerted with the device on the tissue so that it can perform three short pressure applications (15 ms) on the tissue [24]. Myotonometry was performed using the MyotonPro device (MytonPro, Myoton Ltds., Tallinn, Estonia).

2.6. Statistical Analysis

A statistical analysis was performed using SPSS v.26 statistical software. The level of significance was set at $\alpha = 0.05$. The Shapiro-Wilk test was used to assess the normal distribution of the variables. Descriptive statistics were performed for all the variables analyzed. Quantitative variables were expressed by mean and standard deviation (in case of normal distribution) and median and interquartile range (for non-normal dis-tribution). Qualitative or categorical variables were expressed as percentages. To eval-uate the effect of the intervention, due to the sample size, a Wilcoxon test was per-formed using the pre- and post-intervention values.

3. Results

The baseline characteristics of the 16 participants are shown in Table 1. As shown, the majority of the sample (81.25%) were female, with a mean age of 76.5 (7.68) years. The sample had a BMI considered as "normal", and were independent in their daily lives. Moreover, as for the different tests of functionality, in all of them the mean was above the cut-off points. In terms of adherence, the average attendance was 83.5% (12.2). Table 2 shows the changes produced after the intervention both in the functional tests and in the variables related to functional quality.

Table 1. Baseline characteristics of the sample.

Variable	
N (M/F)	16 (3/13)
Age, years	76.5 ± 7.68
Height, cm	151 ± 5.01
Weight, kg	59.6 (10.3) *
BMI, kg/m2	27.6 ± 3.96
Barthel, score	100 (0.0) *
FES-I, score	18 (4.0) *
PASE, score	111 ± 41.3
Attendance, %	83.5 ± 12.2

*, Median (IQR); BMI, Body Mass Index; FES-I, Falls Efficacy Scale-International; PASE, Physical Activity.

Table 2. Difference between baseline and post intervention.

Variable	Baseline	Mean	95% Confidence	Effect	*p*-Value

		Difference	Interval		Size	
			Lower	Upper		
SPPB, score	12 ± 1.0 *	−1.00	–	–	1.00	0.346
5XSST, s	9.47 ± 1.75	1.50	0.10	2.71	0.72	0.027
TUG, s	9.56 ± 2.06	0.94	0.31	1.84	0.95	0.001
Walking Speed, m/s	1.05 ± 0.24	−0.06	−0.13	0.01	0.54	0.110
Handgrip Strength, kg	20.6 ± 7.9 *	−0.35	−2.70	2.33	0.05	0.893
Contraction Time-RA, ms	35.0 ± 7.15 *	2.37	−5.12	14.49	0.28	0.410
Maximal Radial Displacement-RF, mm	3.95 ± 1.95	−0.66	−2.53	0.30	0.51	0.126
Stiffness-RF, N·m^{-1}	307 ± 53.2	7.89	−17.00	33.00	0.24	0.480
Contraction Time-VL, ms	1.77 ± 1.63 *	6.25	−4.15	22.73	0.33	0.327
Maximal Radial Displacement-VL, mm	26.4 ± 18.3 *	0.19	−0.91	1.02	0.15	0.666
Stiffness-VL, N·m^{-1}	318 ± 35.4	29.00	11.00	50.50	0.94	0.007

*, Median (IQR), SPPB, Short Physical Performance Battery; 5XSST, Five Times Sit to Stand Test; TUG, Timed Up and Go test; WS, Walking Speed; HG, Handgrip Strength; Tc, Contraction Time; Dm, Maximal radial displacement; St, Stiffness; RF, Rectus Femoris; VL, Vastus Lateralis.

4. Discussion

The present study aimed to evaluate the changes produced by an MCT program on both physical performance and muscle quality in a population of healthy older adults. The main results of this study show some moderate improvement in physical perfor-mance, but no effect in muscle quality parameters, except for vastus lateralis stiffness.

As already explained in the introductory section, aging involves a series of local and systemic changes, which cause changes in physical performance as well as in muscle strength and quality. Specifically, Jacob et al. [25], concluded that older adults have lower physical performance, as well as longer contraction times and greater mus-cle stiffness.

In fact, loss of physical performance and muscle quality are key factors for the diagnosis of sarcopenia, and are in turn related to frailty and other adverse events, such as falls, loss of dependency and even mortality [26,27]. For its part, the EWGSOP recognizes that "there is no universal consensus on assessment methods for routine clinical practice" [6]. Fabiani et al. [28] propose tools such as tensiomyography as possible solutions to the assessment of muscle quality. Myotonometry is another current alternative in the assessment of muscle quality which provides complementary information to tensiomyography [29,30].

Regarding recommendations on the treatment of sarcopenia, there is a consensus that MCT with an emphasis on resistance training is one of the first-line treatment op-tions [19]. Actually, given the high prevalence of sarcopenia among older adults, some authors have gone so far as to question whether the diagnosis of sarcopenia really matters, arguing that resistance training should be prescribed to that entire population group [31]. However, other authors recognize the particularity of this condition and the need for a specific therapeutic exercise prescription [32].

In view of the results in terms of muscle quality, the question would be whether myotonometry and tensiomyography are the best tools to assess it, or whether other tools such as electromyography, ultrasound or even blood biomarkers could provide us with better information on the state of skeletal muscle. Moreover, there is a need to study the effectiveness of novel training techniques such as blood flow restriction in terms of physical performance and muscle quality, as this could be a good alternative for older adults who cannot tolerate the high loads of conventional resistance training [33], or in combination with nutritional supplements [34].

This study has several limitations. First, the study has a relatively low sample size. In addition, the study lacks a control group, so the observed changes may have been caused by other factors, such as the tendency to decrease physical performance with aging. However, given that trends in physical performance and muscle quality tend to decrease with aging, it is unlikely that the improvements observed are due to other factors. As for the duration of the intervention, it is likely that a longer duration would have led to significant changes in muscle quality variables. Another limitation of the study is that the number of women was significantly higher than that of men. In this sense, it is possible that the results obtained in a population of men would be different. Finally, it is important to highlight that the population studied was older adults with a high level of independence. It is possible that in frail populations or those with comorbidities, the results obtained could be different.

5. Conclusions

MCT is able to generate improvements in the physical performance of older adults, but these improvements are not reflected in muscle quality parameters measured by tensiomyography and myotonometry. Intervention studies are needed with larger populations and control groups, as well as a lower level of functional capacity, in order to perform high intensity training.

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DISCUSIÓN

Como ya se adelantó en el apartado de justificación, los resultados de la presente tesis doctoral pueden diferenciarse en 2 líneas de investigación diferentes, aunque enmarcadas dentro de la función neuromuscular del adulto mayor.

La primera línea de investigación hace referencia a la relación entre la calidad muscular y el desempeño físico durante el envejecimiento. Tal y como recomienda el EWGSOP en su último consenso, es prioritario identificar qué indicadores de calidad muscular predicen mejor la pérdida de fuerza, masa muscular y desempeño físico (105). Del mismo modo, plantea la cuestión de cómo y a través de qué herramientas se puede evaluar de forma precisa y asequible la calidad muscular (105). El principal problema actual se encuentra en la falta de una definición consensuada por la comunidad científica acerca de qué se entiende por calidad muscular (127,171). De hecho, algunos autores han recomendado evitar el uso de este término de manera temporal, ya que consideran que sus diferentes acepciones pueden llevar a confusión (152). Actualmente, la calidad muscular suele referirse principalmente a dos conceptos. El primero hace referencia a la cantidad de fuerza por unidad de masa muscular (119); y el segundo a la composición y características micro- y macroscópicas del músculo (105). En la presente tesis doctoral se ha decidido hacer uso de esta segunda definición, que engloba los cambios en el tamaño muscular, en el tipo de fibra, en el nivel de activación neuromuscular, en la arquitectura del músculo (longitud y ángulo de penación), en la infiltración de tejido adiposo intermuscular y en posibles procesos de fibrosis (223). Estos cambios en la calidad muscular se han descrito en patologías como la sarcopenia y el síndrome de fragilidad (79), sin embargo, su evaluación habitualmente necesita herramientas costosas, que generan irradiación, o que no resultan prácticas en el ámbito clínico (121).

El desarrollo de las nuevas tecnologías ha permitido desarrollar herramientas no-invasivas y con mayor practicidad que podrían cubrir esta necesidad (224,225). Sin embargo, en vista de los resultados de la presente tesis doctoral (proyectos 2 y 3, principalmente) todavía no queda clara su relación con el desempeño físico. A priori, podría pensarse que estos cambios en la calidad muscular podrían tener un impacto en el desempeño físico, sin embargo, no se ha encontrado una correlación significativa entre el desempeño físico medido con los diferentes test funcionales, y la calidad muscular. A pesar de estos resultados, consideramos que las limitaciones metodológicas presentadas en los proyectos podrían haber influido en los resultados obtenidos. En este sentido, como líneas futuras, se plantea incluir en la valoración un espectro de adultos mayores más diverso, en el que se evalúen personas con mayor o menor grado de independencia y desempeño físico, así como adultos mayores con patologías crónicas. Además, tal y como concluyen McGregor y colaboradores (223), resulta indispensable comenzar a evaluar a los adultos de mediana edad, para poder conocer mejor los cambios en la calidad muscular y establecer estrategias centradas no sólo en el tratamiento sino en la prevención tanto primaria como secundaria (223).

La segunda línea de investigación tenía como objetivo evaluar la efectividad de diferentes modalidades de entrenamiento tanto en la mejora de la fuerza muscular como del desempeño físico los adultos mayores. Para ello, se realizó una búsqueda preliminar de la literatura, y con ello se decidió que la mejor manera de responder a los objetivos planteados era mediante la realización de diferentes revisiones sistemáticas y meta-análisis.

Pese a la viabilidad de los meta-análisis realizados, todos ellos cuentan con una serie de limitaciones generales que conviene destacar. La limitación principal reside en la heterogeneidad de los resultados obtenidos en los diferentes estudios que conformaban los meta-análisis que se llevaron a cabo (226). A la hora de explorar la heterogeneidad encontrada, principalmente se debe a dos motivos. El primero podría ser la propia heterogeneidad de la muestra de los estudios. Aunque la muestra estuviese constituida por adultos mayores de 65 años, la media de edad podría diferir significativamente entre estudios. Además, aun teniendo en cuenta que se trataba de adultos mayores sanos, el nivel de independencia y desempeño físico de base podría variar entre ellos (227). El segundo motivo de la heterogeneidad de los resultados podría ser la diferencia en el diseño de los programas de entrenamiento. A pesar de agruparse todos bajo la misma modalidad de entrenamiento (RT, AT, BT, MCT, BFR-t etc.), las variables del entrenamiento diferían entre ellos, tanto en términos de duración del programa, como de intensidad, volumen y frecuencia de entrenamiento (227,228). Todas estas diferencias, afectarían al estímulo de entrenamiento y, por ende, a la respuesta adaptativa del entrenamiento, es decir, en este caso, en las mejoras en la fuerza y desempeño físico observadas.

En este sentido, tal y como afirman Molinero y colaboradores en su artículo sobre la interpretación, utilidad y limitaciones del metaanálisis (229), quizás la utilidad más valiosa de este tipo de estudios no sea establecer un efecto global de las intervenciones, sino explorar las posibles causas de la heterogeneidad de los diferentes estudios y así generar nuevas hipótesis para líneas de investigación futuras.

En la misma línea, durante los últimos años, ha existido un amplio debate acerca de la variabilidad de resultados obtenidos por los individuos de los estudios (230). Algunos investigadores trataron de clasificar como “respondedores” o “no-respondedores” a los individuos según si respondían de manera favorable o no (es decir, o no respondían, o lo hacían de manera negativa) a la intervención llevada a cabo (231). Sin embargo, tal y como se argumenta en el artículo de Pickering y colaboradores (232), utilizar esta terminología en los estudios en los que se realiza una intervención mediante ejercicio físico, presenta una serie de inconvenientes. En primer lugar, la respuesta ante cualquier intervención no se puede dicotomizar en dos categorías, como el caso de “respondedores” o “no-respondedores”, sino que la respuesta se presenta en forma de espectro de valores. Así pues, algunos investigadores prefieren utilizar el término de individuos con “alta o baja sensibilidad” a la intervención (231). Por otra parte, estos términos se presentan como una condición fija de cada individuo, sin embargo, no está claro que la respuesta de un individuo ante un mismo estímulo sea siempre la misma (232). Además, tal y como se ha tratado de reflejar en el apartado de introducción, el ejercicio físico genera una respuesta fisiológica que involucra de manera coordinada a numerosos sistemas del organismo (233). Sin embargo, en la mayoría de ensayos clínicos, por razones de viabilidad, únicamente se miden una serie de variables concretas, y resulta imposible medir todas las adaptaciones potencialmente generadas por el ejercicio físico. De esta manera, categorizar como “respondedor” o “no-respondedor” al ejercicio físico a un individuo, únicamente teniendo en cuenta unas pocas variables es reduccionista (232). Finalmente, existen diferentes estudios que han tratado de desmitificar la idea de la existencia de personas “no-respondedoras” al ejercicio físico en diferentes condiciones (234–236). En estos estudios, se realiza una intervención determinada de ejercicio físico, y tras ella, se identifica a aquellos individuos que tienen una menor respuesta ante la intervención. A continuación, se realiza una modificación en su intervención y se continua la misma, de tal manera que al final de la segunda intervención, la gran mayoría de los individuos generan adaptaciones positivas al ejercicio. Las estrategias de modificación de la intervención pueden ser desde las más sencillas, como aumentar la duración de la intervención (es decir, prolongar la misma unas sesiones más) (236), aumentar el volumen (nº de repeticiones, de series o de tiempo de entrenamiento) (234,237), o aumentar la intensidad del entrenamiento (238). Como estrategias más complejas, podrían considerarse variar la modalidad de entrenamiento (239) o añadir estrategias “coadyudantes”, que ejerzan un efecto sinergista con la intervención principal (230). En resumen, la evidencia actual parece indicar que no existen personas “no-respondedoras” al ejercicio físico, sin embargo, tanto la hora de diseñar los programas de entrenamiento como a la hora de plantear las progresiones, se debería tender a individualizarlo a cada persona, de tal manera que cada una reciba la dosis adecuada de estímulo que maximice los beneficios del entrenamiento y disminuya los posibles efectos adversos (230). Evidentemente, esta tarea se dificulta en el ámbito residencial u hospitalario, donde el volumen de pacientes es habitualmente elevado, y la individualización de los programas de ejercicio terapéutico resulta más complicada. Para solucionar esta limitación, algunos investigadores han tratado de establecer estrategias para estratificar a los individuos en diferentes niveles previamente a la intervención, a través de la valoración del desempeño físico (240,241). De esta manera, pretenden identificar a los potenciales "no-respondedores" y adaptar el programa de entrenamiento para que todos puedan resultar beneficiados (235,241).

Como reflexión personal, quizás las futuras líneas de investigación no se deberían centrar tanto en comparar la efectividad de diferentes modalidades de entrenamiento, sino tal vez en estudiar la manera de identificar a aquellos pacientes que se puedan beneficiar más de un tipo de intervención o u otra, y realizar estudios con programas de entrenamiento individualizados.

La segunda limitación importante de las revisiones sistemáticas es que la población de estudio son personas consideradas "sanas". Esta condición excluye pacientes que potencialmente se podrían beneficiar de las intervenciones de ejercicio terapéutico en sus diferentes modalidades (199). Entre ellas, dada su alta prevalencia entre los adultos mayores, podrían destacar la sarcopenia y el síndrome de fragilidad. Sin embargo, existe una problemática en el campo de investigación actual en el adulto mayor. Con la tendencia de obtener una muestra similar que garantice unos resultados homogéneos, la mayoría de estudios sobre ejercicio físico en adulto mayor excluyen a personas con patologías, como es el caso del síndrome de fragilidad (242). Sin embargo, son precisamente este tipo de personas las que más necesitan estas intervenciones. Esta falta de investigación genera desconocimiento en el ámbito clínico, donde los profesionales de la salud desconocen cómo va a responder su paciente ante un determinado tratamiento, o cuales son las mejores estrategias que deberían llevar a cabo. También en esa línea, los últimos consensos en sarcopenia han coincidido en que es necesaria más investigación en esta patología, tanto para seguir conociendo su prevalencia y su fisiopatología, como para establecer qué intervenciones son las más efectivas para contrarrestar las disfunciones asociadas a la misma (105,113,115,116).

Mención especial debe realizarse a un artículo que realizaron el año 2022 varios investigadores australianos al respecto de la prescripción de ejercicio terapéutico en el adulto mayor (243). En él, hablaban de la importancia del entrenamiento de fuerza en la población general de adultos mayores, y argumentaban que, a su parecer, las recomendaciones acerca del mismo eran muy similares a las de los adultos mayores con sarcopenia (243). En este sentido, opinaban que el diagnóstico de la sarcopenia carecía de relevancia clínica, y que todos los adultos mayores, independientemente de que padeciesen sarcopenia o no, debían incorporar en su día a día ejercicios de fortalecimiento muscular. Así pues, los esfuerzos de la comunidad científica no deberían centrarse tanto en desarrollar consensos sobre el diagnóstico de la sarcopenia, sino en optimizar los programas de entrenamiento, y generar adherencia a largo plazo (243).

Como respuesta, otro grupo de investigadores, en este caso italianos, publicó un artículo en la misma revista refutando las ideas planteadas en la obra anterior (203). Argumentaron que la sarcopenia estaba catalogada como una enfermedad según el ICD-10, y que, por tanto, era necesario invertir recursos en generar un consenso común que permitiese diagnosticar y abordar la patología entre diferentes profesionales de la salud (203). Dicho esto, reconocían que, actualmente, no existía un consenso claro en torno a ello, dada la falta de estudios sobre la sarcopenia por los motivos expuestos anteriormente (exclusión de las personas con esta condición de los ensayos clínicos en adultos mayores) (203). A pesar de la falta de estudios, entendían que la sarcopenia era una patología compleja y de carácter multifactorial, asociada habitualmente a otras comorbilidades. Por todo esto, consideraban que la respuesta de las personas con sarcopenia ante un mismo estímulo pudiera ser completamente diferente a la de un adulto mayor considerado como sano (203). Los adultos mayores diagnosticados con sarcopenia requieren de una mayor atención en la dosificación de las cargas mediante la manipulación de las variables de entrenamiento (intensidad, volumen frecuencia, descanso etc.), así como posibles adaptaciones en la selección de ejercicios o en la educación en el dolor muscular tras la sesión (204).

Recogiendo todas estas ideas, tras haber realizado la presente tesis doctoral, considero que resulta imprescindible seguir estudiando esta condición, tanto en su fisiopatología, como en su diagnóstico y en la eficacia de las diferentes modalidades de ejercicio terapéutico. Todo esto debería realizarse sin perder de vista la realidad clínica de los fisioterapeutas, en la que tal vez los recursos (ya sea en tiempo, material o personal) puedan suponer una limitación a la hora de poner en práctica los nuevos avances que se realicen en este campo.

CONCLUSIONES

Los resultados obtenidos en los diferentes proyectos han permitido extraer las siguientes conclusiones:

- Existe una correlación débil entre el máximo desplazamiento radial (Dm), valorado mediante TMG y el stiffness, valorado mediante MMT.

- Existe una correlación positiva moderada estadísticamente significativa entre la batería SPPB y el Dm de la musculatura recto femoral y vasto lateral cuádriceps.
- Existe una correlación negativa débil estadísticamente significativa entre la prueba 5XSST y el Dm de la musculatura recto femoral y vasto lateral del cuádriceps. No se encontraron correlaciones estadísticamente significativas entre el Dm y el resto de test funcionales analizados.
- Existe una correlación negativa débil estadísticamente significativa entre la prueba 5XSST y la rigidez del vasto lateral del cuádriceps. No se encontraron correlaciones estadísticamente significativas entre el stiffness y el resto de test funcionales analizados.
- No existe significancia estadística entre el tiempo de contracción (Tc) y los test funcionales de SPPB, TUG, 5XSST, velocidad de marcha en 4 metros, fuerza de agarre y fuerza de extensión de rodilla.

- Existe una correlación débil estadísticamente significativa entre la superficie de la elipse del estabilograma, valorada con los ojos abiertos, y los test funcionales de SPPB, 5XSST y velocidad de marcha en 4 metros.

- Existe una correlación moderada estadísticamente significativa entre la longitud del estabilograma, valorada con los ojos abiertos, y los test funcionales de SPPB, 5XSST y velocidad de marcha en 4 metros. La correlación con la prueba TUG es débil.
- Existe una correlación moderada estadísticamente significativa entre la superficie de la elipse del estabilograma, valorada con los ojos cerrados, y los test funcionales de SPPB y 5XSST.
- Existe una correlación moderada estadísticamente significativa entre la longitud del estabilograma, valorada con los ojos cerrados, y los test funcionales de SPPB y 5XSST. La correlación con las pruebas TUG y la velocidad de marcha en 4 metros es débil.

- No existen diferencias significativas entre la combinación de entrenamiento de fuerza (RT) más suplementación proteica (PS), y el entrenamiento de fuerza en solitario en la mejora de la fuerza muscular ni el desempeño físico en adultos mayores sanos.

- El BFRt mejora la fuerza muscular de manera estadísticamente significativa.
- El BFRt no mejora el desempeño físico de manera estadísticamente significativa.

- El MCT mejora la el desempeño físico, la fuerza en las extremidades superiores e inferiores, la velocidad de la marcha y la capacidad aeróbica en adultos mayores sanos.

- Las diferentes modalidades de entrenamiento (entrenamiento de fuerza, entrenamiento aeróbico, entrenamiento de equilibrio y entrenamiento multicomponente) no mejoran el equilibrio estático de manera estadísticamente significativa.

- Un programa de MCT genera mejoras estadísticamente significativas en las pruebas funcionales de 5XSST, velocidad de marcha en 4 metros y fuerza de agarre.
- Un programa de MCT no genera mejoras estadísticamente significativas en los parámetros obtenidos mediante TMG en la musculatura de vasto lateral y recto anterior del cuádriceps.
- Un programa de MCT genera mejoras estadísticamente significativas en el stiffness del vasto lateral.

CONCLUSIONS

The results obtained from the different projects have led to the following conclusions:

- There is a weak correlation between maximum radial displacement (Dm), assessed by TMG, and stiffness, assessed by MMT.

- There is a statistically significant moderate positive correlation between the SPPB battery and Dm of the rectus femoris and vastus lateralis muscles.
- There is a statistically significant weak negative correlation between the 5XSST test and Dm of the rectus femoris and vastus lateralis muscles. No statistically significant correlations were found between Dm and the rest of the analyzed functional tests.
- There is a statistically significant weak negative correlation between the 5XSST test and the stiffness of the vastus lateralis muscle. No statistically significant correlations were found between stiffness and the rest of the analyzed functional tests.
- There is no statistical significance between contraction time (Tc) and the SPPB, TUG, 5XSST, 4-meter walking speed, grip strength, and knee extension strength tests.

- There is a statistically significant weak correlation between the surface area of the stabilogram ellipse, evaluated with eyes open, and the SPPB, 5XSST, and 4-meter walking speed tests.

- There is a statistically significant moderate correlation between the length of the stabilogram, evaluated with eyes open, and the SPPB, 5XSST, and 4-meter walking speed tests. The correlation with the TUG test is weak.
- There is a statistically significant moderate correlation between the surface area of the stabilogram ellipse, evaluated with eyes closed, and the SPPB and 5XSST tests.
- There is a statistically significant moderate correlation between the length of the stabilogram, evaluated with eyes closed, and the SPPB and 5XSST tests. The correlation with the TUG and 4-meter walking speed tests is weak.

- There are no significant differences between the combination of resistance training (RT) and protein supplementation (PS) and resistance training alone in improving muscle strength or physical performance in healthy older adults.

- Blood flow restriction training (BFRt) improves muscle strength in a statistically significant way.
- BFRt does not improve physical performance in a statistically significant way.

- Multicomponent training (MCT) improves physical performance, upper and lower limb strength, walking speed, and aerobic capacity in healthy older adults.

- Different training modalities (resistance training, aerobic training, balance training, and multicomponent training) do not significantly improve static balance.

- An MCT program generates statistically significant improvements in the 5XSST, 4-meter walking speed, and grip strength functional tests.
- An MCT program does not generate statistically significant improvements in the parameters obtained by TMG in the vastus lateralis and rectus femoris muscles.
- An MCT program generates statistically significant improvements in the stiffness of the vastus lateralis muscle.

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ANEXOS

Carta de aprobación del comité de ética de investigación

APROVACIÓ PROJECTE PEL CER/ APROBACIÓN PROYECTO POR EL CER

Codi de l'estudi / *Código del estudio*: CBAS-2020-12
Versió del protocol / *Versión del protocolo*: 2.0
Data de la versió / *Fecha de la versión*: 20/11/20

Sant Cugat del Vallès, 27 de setembre de 2021

Doctorand/o: Noé Labata Lezaun
Directors/es: Dr. Albert Pérez Bellmunt, Dra. Vanessa González Rueda
Títol de l'estudi / ***Título del estudio*****:** Análisis de la función neuromuscular en persones ancianas

Benvolgut/da,

Valorat el projecte presentat, el CER de la Universitat Internacional de Catalunya, considera que, el contingut de la investigació, no implica cap inconvenient relacionat amb la dignitat humana, tracte ètic per als animals ni atempta contra el medi ambient, ni té implicacions econòmiques ni conflicte d'interessos, no s'han valorat els aspectes metodològics sense implicacions ètiques del projecte de recerca, degut a que tal anàlisis correspon a d'altres instàncies

Per aquests motius, el Comitè d'Ètica de Recerca, RESOLT FAVORABLEMENT, emetre aquest CERTIFICAT D'APROVACIÓ, per que pugui ser presentat a les instàncies que així ho requereixin.

Em permeto recordar-li que, si en el procés d'execució es produís algun canvi significatiu en els seus plantejaments, hauria de ser sotmès novament a la revisió i aprovació del CER.

Atentament,

Apreciado/a,

Valorado el proyecto presentado, el CER de la Universidad Internacional de Catalunya, considera que, el contenido de la investigación, no implica ningún inconveniente relacionado con la dignidad humana, trato ético para los animales, ni atenta contra el medio ambiente, ni tiene implicaciones económicas ni conflicto de intereses, pero no se han valorado aspectos metodológicos sin implicaciones éticas del proyecto de investigación, debido a que tal análisis corresponde a otras instancias.

Por estos motivos, el Comitè d'Ètica de Recerca, RESUELVE FAVORABLEMENTE, emitir este CERTIFICADO DE APROBACIÓN, para que pueda ser presentado a las instancias que así lo requieran.

Me permito recordarle que, si el proceso de ejecución se produjera algún cambio significativo en sus planteamientos, debería ser sometido nuevamente a la revisión y aprobación del CER.

Atentamente,

Secretaria CER-UIC

NOGALES GADEA NOELIA - 53288914F

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Consentimiento Informado

<u>DOCUMENTO DE INFORMACIÓN AL SUJETO PARTICIPANTE DEL ESTUDIO DE INVESTIGACIÓN</u>

Código del protocolo de investigación:
Versión del protocolo: 1
Fecha de la versión del protocolo:
Fecha de la presentación del protocolo:
Título del Proyecto: Análisis de la función neuromuscular en personas ancianas

1.	Director/a del Proyecto: Dr. Albert Pérez Bellmunt y Dra. Vanessa González Rueda
2.	Investigador/a: Noé Labata Lezaun
3.	Departamento: Ciencias Básicas. Unidad de Anatomía

Hemos solicitado su participación en un estudio de investigación. Antes de decidir si aceptan participar, es importante que comprendan los motivos por los cuales se lleva a cabo la investigación: como se usará su información, en qué consistirá el estudio y los posibles beneficios, riesgos y molestias que pueda comportar.

En caso que participen en algún otro estudio, lo tendrán que comunicar al responsable para valorar si pueden participar en este.

¿CUALES SON LOS ANTECEDENTES Y EL OBJETIVO DE ESTE ESTUDIO?

Se trata de un estudio pionero cuyo objetivo es valorar el nivel de correlación entre las diferentes pruebas de medición de la función neuromuscular y los cuestionarios y pruebas de ejecución utilizados habitualmente en la práctica clínica para valorar el nivel de funcionalidad en las personas ancianas.

¿TENGO LA OBLIGACIÓN DE PARTICIPAR?

La decisión sobre participar o no en la investigación corresponde a ustedes. En el caso en que no quieran participar o bien quieran abandonar, la cualidad de la asistencia que reciban no se verá afectada. Si deciden participar, les pasaremos un formulario de consentimiento informado para que lo firmen.

¿CUALES SON MIS OBLIGACIONES?

- Rellenar las escalas de independencia (Barthel), fragilidad (FRAIL, FES-I) y actividad física (PASE).
- Valoración de la composición corporal.
- Valoración del tejido muscular en las extremidades inferiores (TMG y MMT).
- Medición de la fuerza isométrica máxima para varios movimientos del miembro inferior.
- Realizar una batería de test funcionales (SPPB y TUG) monitorizadas mediante electromiografía.
- Medición de la fuerza de agarre.
- Realizar una prueba de equilibrio con ojos abiertos y cerrados.

¿CUALES SON LOS POSIBLES EFECTOS SECUNDARIOS, RIESGOS Y MOLESTIAS ASOCIADOS A LA PARTICIPACIÓN?

Ninguno de los procedimientos que se le aplicarán representa riesgo para su salud. No tiene efectos secundarios, ni adversos aparte de los derivados de la práctica de ejercicio físico. Todas las pruebas son inocuas.

¿CUALES SON LOS POSIBLES BENEFICIOS DE PARTICIPAR?

Al ser un estudio observacional, no recibirá ningún tipo de beneficio directo. Sin embargo, con su participación, usted ayudará a hacer ciencia y a generar nuevos conocimientos. Su ayuda permitirá conocer mejor la relación entre diferentes parámetros de la función neuromuscular y la funcionalidad, lo que permitiría tratar de reducir, entre otros, el riesgo de sufrir caídas.

¿COMO SE UTILIZARÁN MIS DATOS EN EL ESTUDIO?

El trato, la comunicación y la cesión de los datos de carácter personal de los sujetos participantes en el ensayo se ajustan a lo que dispone la Ley orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales.
Estos datos, no incluyen ni su nombre ni su dirección, sino que se le asignará un número de código. Únicamente el equipo investigador, tendrá acceso a la clave del código que permite asociar los datos del estudio con ustedes. No obstante, las autoridades reguladoras, el comité de ética independiente u otras entidades de supervisión podrán revisar sus datos personales. El objetivo de dichas revisiones es garantizar la dirección adecuada del estudio o la cualidad de los datos del estudio.

Si retiran del consentimiento informado de usar sus datos para el estudio, no podrán continuar participando en la investigación. Han de tener en cuenta que los resultados del estudio pueden aparecer publicados en la bibliografía, si bien, su identidad no será revelada.

¿COMO PUEDO ESTABLECER CONTACTO SI NECESITO OBTENER MÁS INFORMACIÓN O AYUDA?

Mediante la firma de este formulario, asienten que han sido informados de las características del estudio, han entendido la información i se les ha clarificado todas sus dudas.

En caso de padecer un daño relacionado con el estudio o para obtener respuesta a cualquier pregunta que pueda surgir durante la investigación contacte con:

Dr. Albert Pérez Bellmunt
Nº de teléfono: 636 817 297
Correo electrónico: aperez@uic.es

Noé Labata Lezaun
Nº de teléfono: 633 34 68 24
Correo electrónico: nlabata@uic.es

Universitat Internacional de Catalunya
Dirección: C/ Josep Trueta, s/n, 08195, Sant Cugat del Vallès
Nº de teléfono: 93 504 20 00 Ext: 5261

CONSENTIMENTO INFORMADO DOCUMENTO DE INFORMACIÓN AL SUJETO

PARTICIPANTE DEL ESTUDIO DE INVESTIGACIÓN

CONSENTIMENTO INFORMADO

Código del estudio:
Versión del protocolo: 1
Fecha de la versión:
Fecha de la presentación:
Título del Proyecto: Análisis de la función neuromuscular en personas ancianas

4.	Director/a del Proyecto: Dr. Albert Pérez Bellmunt y Dra. Vanessa González Rueda
5.	Investigador/a: Noé Labata Lezaun
6.	Departamento: Ciencias Básicas. Unidad de Anatomía

Yo, el Sr./la Sra: ……………………………………………………………….

- He recibido información verbal sobre el estudio y he leído la información escrita que se adjunta, la cual me ha sido facilitada una copia.
- He comprendido lo que se me ha explicado y los posibles riesgos y beneficios de participar en el estudio.
- He podido comentar el estudio y hacer preguntas al profesional responsable.
- Doy mi consentimiento para tomar parte en el estudio y asumo que mi participación es totalmente voluntaria.
- Entiendo que me podré retirar en cualquier momento.

Mediante la firma de este formulario de consentimiento informado, doy mi conformidad para que mis datos personales se puedan usar como se ha descrito en este formulario de consentimiento, que se ajusta a lo que dispone la Ley orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales.

Entiendo que recibiré una copia de este formulario de consentimiento informado.

_________________________ _________________________

Firma del Participante — Fecha de la firma
Núm. de DNI

_________________________ _________________________

Firma del Investigador/a — Fecha de la firma
Nombre: