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Facultad de Farmacia y Nutrición

Influencia de la situación de desnutrición e impacto de la suplementación nutricional oral sobre la salud muscular y la mortalidad en personas mayores con fractura de cadera

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Vincenzo Malafarina

El presente trabajo ha sido realizado bajo mi dirección en el Departamento de Ciencias de la Alimentación y Fisiología de la Facultad de Farmacia y Nutrición de la Universidad de Navarra y autorizo su presentación ante el Tribunal que lo ha de juzgar.

Pamplona, de de 2019

VºBº Directora

Prof. Mª Ángeles Zulet Alzórriz

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Resumen

Introducción: La sarcopenia es un síndrome geriátrico caracterizado por la pérdida progresiva de masa, fuerza y función muscular, reconocido por la Organización Mundial de la Salud como una enfermedad (M62.84). El algoritmo propuesto por el grupo europeo de trabajo sobre la sarcopenia en las personas mayores (*European Working Group on Sarcopenia in Older People*, EWGSOP) coloca la medición de la fuerza muscular como primer paso para el diagnóstico de sarcopenia, seguido en caso de resultar positivo de la medición de la cantidad y calidad muscular. La prevalencia aumenta con la edad y se asocia con un aumento del riesgo de desarrollar discapacidad física y mortalidad, así como con desnutrición. El tratamiento de la sarcopenia se basa en la combinación de dieta (aumento de la ingesta proteico- calórica y suplementación de vitamina D cuando es requerido) junto con pautas de ejercicio físico.

Hipótesis y objetivos: La hipótesis de este proyecto de investigación es que el estado nutricional y la salud muscular influyen sobre la recuperación tras una fractura de cadera y sobre la mortalidad. En este sentido, se espera que el tratamiento rehabilitador asociado a la suplementación nutricional mejore la recuperación funcional y la situación de desnutrición en los pacientes mayores con fractura de cadera. El objetivo de esta investigación es evidenciar el estado nutricional de las personas mayores con fractura de cadera y valorar cómo influyen la suplementación nutricional y la rehabilitación física sobre la recuperación funcional y sobre el estado nutricional. Las actuaciones estarán encaminadas a evaluar la salud muscular (sarcopenia) y su impacto sobre la evolución funcional y la mortalidad en estos pacientes. Los objetivos específicos de este proyecto de investigación son:

(1) Describir cómo el estado nutricional y la intervención nutricional influyen sobre la evolución clínica y la mortalidad en las personas mayores con fractura de cadera (Capítulo 1);

(2) Valorar si la suplementación nutricional oral enriquecida en β-hydroxi-β-metil-butirato (HMB) y vitamina D, mejora la masa muscular y marcadores del estado nutricional (índice de masa muscular, IMC, y las proteínas totales plasmáticas) en los pacientes mayores con fractura de cadera (Capítulo 2);

(3) Identificar los factores asociados con la presencia de sarcopenia al ingreso (sarcopenia crónica) y con el desarrollo de sarcopenia durante la estancia hospitalaria (sarcopenia incidente) en pacientes de edad avanzada con fractura de cadera, e investigar la influencia de la sarcopenia sobre el riesgo de mortalidad durante 7 años de seguimiento (Capítulo 3).

Métodos: Para alcanzar los objetivos específicos planteados, se ha realizado una revisión científica, y se han evaluado dos poblaciones específicas: estudio HIPERPROT-GER (intervención hiperproteica en pacientes con fractura de cadera) y estudio PREFISSARC-GER (PREvalencia y FISiopatología de la SARCopenia en pacientes con fractura de cadera).

Resultados: En relación al primer objetivo los resultados demuestran que en los pacientes con fractura de cadera la prevalencia de desnutrición es muy alta (siendo casi del 46%), y que esta se asocia con un riesgo aumentado de complicaciones y peor recuperación funcional. La desnutrición, independientemente del criterio utilizado para su definición, se asocia con un aumento de la mortalidad. La intervención nutricional mejora los parámetros nutricionales y se asocia con una mayor recuperación funcional tras la fractura de cadera. En relación al segundo objetivo los resultados obtenidos demuestran que una dieta enriquecida en HMB y vitamina-D mejora la masa muscular, y previene la perdida de peso en pacientes mayores con fractura de cadera. Respecto al tercer objetivo los factores de riesgo asociados con la sarcopenia incidente y crónica fueron el IMC y el MNA-SF, la fuerza de prensión de la mano y el índice de masa muscular esquelética. Durante el seguimiento, murieron 114 pacientes (sarcopénicos 60,5% *vs* no sarcopénicos 39,5%, p = 0,001). El análisis de regresión de Cox mostró que los factores asociados con un mayor riesgo de mortalidad fueron la sarcopenia (HR 1,67, IC 95% 1,11-2,51) y la fuerza de prensión disminuida (HR 1,76, IC 95% 1,08-2,88).

Conclusiones: La literatura científica pone de manifiesto la alta prevalencia de desnutrición en personas mayores con fractura de cadera. Las fracturas de cadera siguen siendo una causa importante de discapacidad, institucionalización y mortalidad prematura. El músculo es un importante marcador del estado nutricional reconociendo la mala salud muscular como el principal factor asociado a las caídas. La suplementación nutricional oral

enriquecida en HMB y vitamina-D evita la perdida de peso y mejora la masa muscular en las personas mayores con fractura de cadera. Los pacientes mayores con desnutrición mostraron mayor riesgo de desarrollar sarcopenia durante la estancia hospitalaria. Además los pacientes sarcopénicos presentaron dos veces mayor riesgo de mortalidad que los pacientes no sarcopénicos durante el seguimiento tras una fractura de cadera. Por todo ello podemos concluir que, la prevención de la desnutrición podría contribuir en reducir la incidencia de fractura, que la suplementación nutricional contribuye en prevenir la perdida de peso y en mejorar la masa muscular tras una fractura de cadera, y en último que la sarcopenia se asocia con un aumento de la mortalidad tras una fractura de cadera.

Investigaciones futuras se deberían centrar en valorar si la reversión de la sarcopenia garantiza una vida libre de discapacidad física así como una reducción de la mortalidad en este tipo de pacientes.

ÍNDICE

1 INTRODUCCIÓN

Sarcopenia

1.1 Definición y diagnosis

La sarcopenia es un síndrome geriátrico caracterizado por la pérdida progresiva de masa, fuerza y función muscular (Cruz-Jentoft et al., 2010b). El término sarcopenia deriva de las palabras griegas “sarx” que significa carne, y “penia” que significa pérdida (Rosenberg, 1989). La sarcopenia es una enfermedad muscular progresiva y generalizada asociada a la edad (sarcopenia primaria) la cual puede empeorar por factores que aceleren la pérdida muscular (Tabla 1), como un estilo de vida sedentario (sarcopenia secundaria) (Malafarina et al., 2012).

Tabla 1. Causas frecuentes de sarcopenia (de Cruz-Jentoft y Sayer, 2019).

Nutricionales:
- Baja ingesta proteica
- Baja ingesta energética
- Déficit de micronutrientes
- Mala-absorción u otra patología gastrointestinal
- Anorexia (asociada a la edad o a mala salud buco dental)

Asociadas con la inactividad:
- Encamamiento, inmovilidad, decondicionamiento
- Baja actividad física, estilo de vida sedentario

Enfermedades:
- De los huesos y articulaciones
- Cardiorrespiratorias
- Metabólicas o endocrinológicas
- Neurológicas
- Cáncer
- Del hígado o de los riñones

Yatrogénicas:
- Hospitalización
- Asociadas a fármacos.

A partir de los 40 años de edad, aproximadamente, se asiste a una pérdida progresiva de masa muscular, calculada en alrededor del 8% por cada década hasta los 70 años, después de los cuales la pérdida aumenta hasta un 15% por década (Grimby et al., 1982; Grimby and Saltin, 1983; Janssen et al., 2000; Larsson et al., 1979; Short et al., 2005). La pérdida de masa muscular es mayor en los varones respecto a las mujeres (Doherty, 2003; Iannuzzi-Sucich et al., 2002; Newman et al., 2005; Zinna y Yarasheski, 2003). Además con la edad se observa la pérdida de fuerza estimándose entre un 10 y un 15% por década hasta los 70 años, pudiendo alcanzar entre el 25-40% de pérdida de fuerza muscular por década pasados los 70 años (Figura 1) (Goodpaster et al., 2006; Hughes et al., 2001; Masanes et al., 2012). Todo esto puede determinar una reducción de la movilidad y una peor calidad de vida (Morley et al., 2011) .

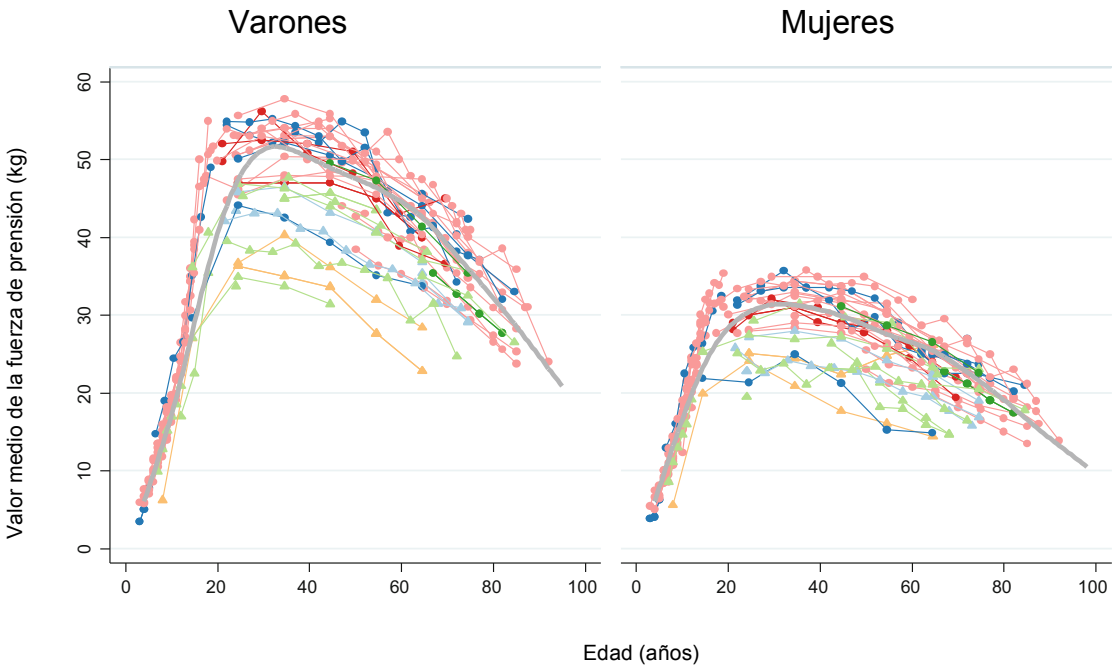

Figura 1. Valor medio de fuerza de prensión de la mano, en varones y mujeres. En amarillo la población africana, en azul oscuro norte americana, en azul claro América excluida la del norte, rosa europea, verde asiática y roja australiana (Shaw et al., 2017).

Los factores que influyen en el desarrollo de la sarcopenia son múltiples (Figura 2) y se debería sospechar de la presencia de sarcopenia en todos aquellos sujetos con síntomas o signos de fallo muscular, como caídas, cansancio, caminar lento, dificultad para levantarse de la silla o pérdida de peso no deseada.

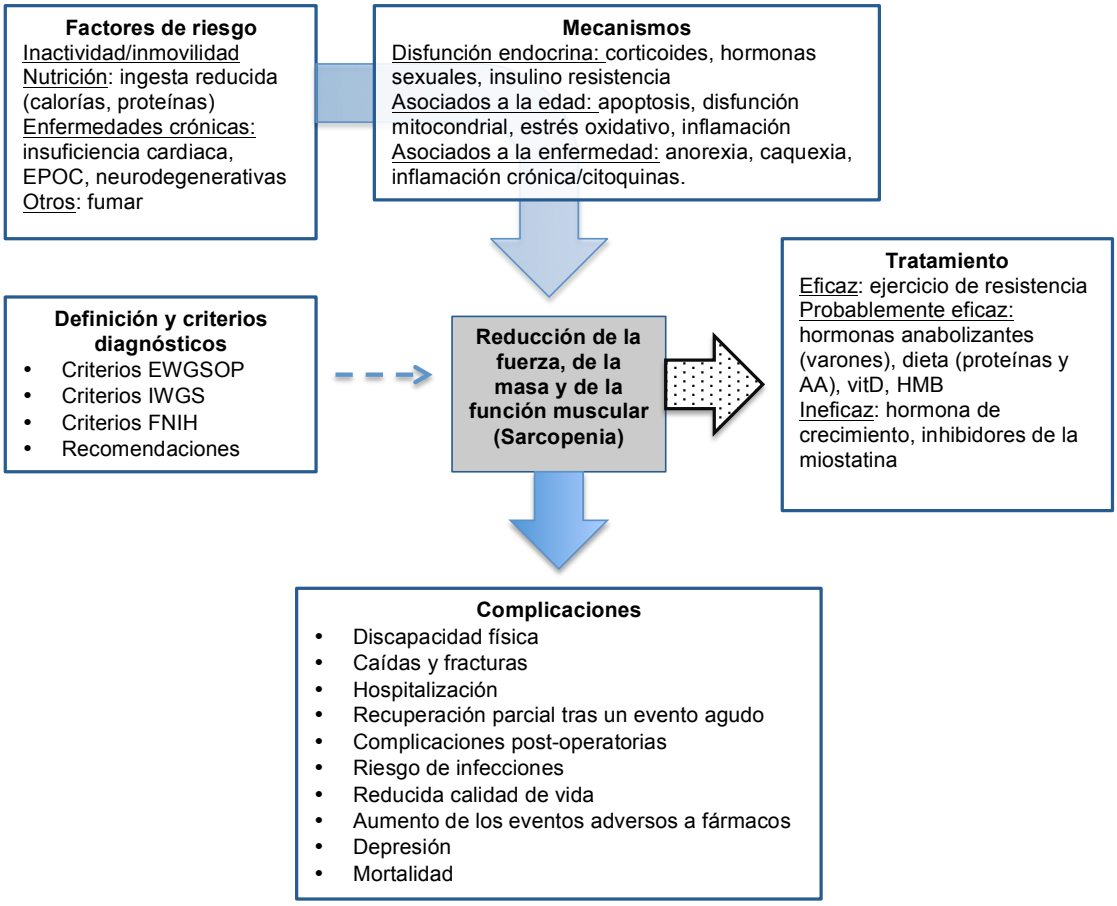

Figura 2. Sarcopenia: factores de riesgo, diagnóstico, complicaciones y tratamiento en las personas mayores (Sloane et al., 2019).
AA: amino-ácidos: AWGS: *Asian Working Group on Sarcopenia*; EPOC: enfermedad pulmonar crónica obstructiva; EWGSOP: *European Working Group on Sarcopenia in Older People*; FNIH: *Fundation National Institute of Health*; HMB: β-hidroxi β-metil butirato; VitD: 25OH-vitaminaD.

La sarcopenia representa un problema clínico de gran envergadura asociado al progresivo envejecimiento de la población. De hecho, las estimaciones de la Unión Europea indican que el número de personas mayores de 65 años incrementará del 17% (en el año 2009) al 30% para el año 2060, y del 5 al 12% en el caso de los mayores de 80 años (European Commission,

2018). Los estudios que han valorado los costes asociados a la sarcopenia, han demostrado cómo la presencia de esta última se asocia con un aumento del gasto sanitario (Bruyère et al., 2019; Janssen et al., 2004b).

En 2010 el grupo europeo para el estudio de la sarcopenia en las personas mayores (EWGSOP: *European Working Group on Sarcopenia in Older People*) propuso un algoritmo diagnóstico que ha sido revisado y actualizado en 2019 (Cruz-Jentoft et al., 2019, 2010a).

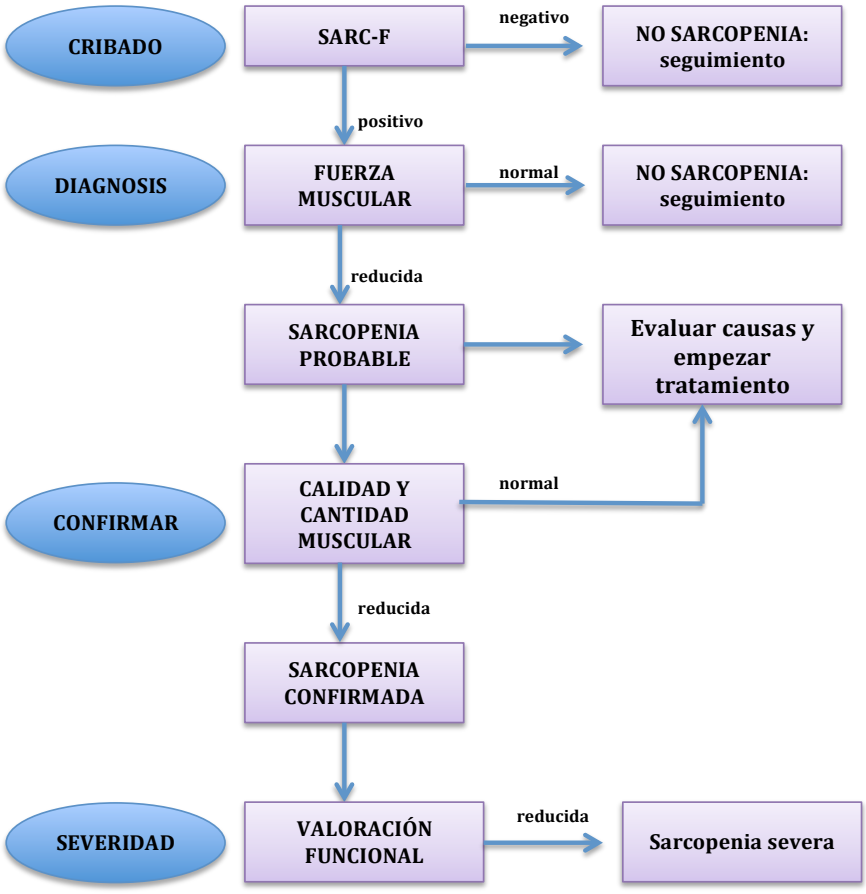

Figura 3. Algoritmo para el diagnóstico de sarcopenia propuesto y actualizado por el grupo europeo de estudio de la sarcopenia en las personas mayores (EWGSOP) (de Cruz-Jentoft et al., 2019).

El algoritmo propuesto y actualizado por el EWGSOP está aceptado para el diagnóstico de la sarcopenia (Figura 3). Dicho algoritmo empieza con el cribado de sarcopenia en las personas que presentan síntomas de bajo rendimiento muscular como caídas, cansancio, lentitud de la marcha o

dificultad para llevar a cabo las actividades de la vida diaria. Para el cribado se aconseja utilizar la escala validada SARC-F (Malmstrom y Morley, 2013). Si el cribado es positivo se aconseja la medición de la fuerza muscular, mediante la utilización de un dinamómetro o bien mediante la valoración de la capacidad de levantarse de la silla sin utilizar las manos.

En el caso de observarse un nivel de fuerza dentro del rango establecido se considera ausente la sarcopenia, aconsejando el seguimiento en el tiempo. Sin embargo si la fuerza observada es menor a la que cabría esperar, para la confirmación del diagnóstico de sarcopenia es necesario la medida de la masa muscular mediante *dual-energy X-ray absorptiometry* (DXA), bioimpedanciometría (BIA), tomografía computarizada (TC) o resonancia magnética (RM). Se aconseja corregir el valor de la masa muscular por la talla, calculando el índice de masa muscular apendicular (Gould et al., 2014). La TC y la RM son los *gold estándar* para la medición de la masa muscular, sin embargo no son técnicas de rutina y no están indicadas en atención primaria, por su elevado coste. El equipo DXA es algo más accesible, aún así no es una técnica de rutina para la determinación de la composición corporal en atención primaria y su coste sigue siendo bastante elevado a la vez que la disponibilidad limitada. La BIA mide la masa muscular de forma indirecta, a través de fórmulas matemáticas, las cuales han sido validadas en diferentes tipos de población (Sergi et al., 2015; Yamada et al., 2017).

Tras la valoración de la fuerza y de la masa muscular, se debe completar el diagnóstico valorando la severidad de la sarcopenia mediante la medición de la capacidad funcional. Para ello se dispone de varios test validados. El test de la velocidad de la marcha de 4 metros es rápido de realizar, altamente sugestivo de sarcopenia y ampliamente utilizado (Cruz-Jentoft et al., 2010a; Studenski et al., 2011). Como alternativa se puede realizar el *Short Physical Performance Battery* (SPPB) (Pavasini et al., 2016), o el test de levantarse y andar (Bischoff et al., 2003), o la capacidad de caminar 400 metros (Newman et al., 2006).

Los puntos de corte propuestos para el diagnóstico de sarcopenia se presentan en la Tabla 2.

Tabla 2. Puntos de corte para el diagnóstico de sarcopenia propuestos por el EWGSOP (Cruz-Jentoft et al., 2019).

Prueba	Puntos de corte varones	Puntos de corte mujeres	Referencias
Puntos de corte para definir fuerza reducida según sentadillas y dinamómetro			
Dinamómetro	<27kg	<16kg	Dodds et al., 2014
Sentadillas	>15 s para cinco repeticiones		Cesari et al., 2009
Puntos de corte para definir baja masa muscular			
ASM	<20kg	<15kg	Studenski et al., 2014
ASM/talla^2	<7,0 kg/m^2	<5,5 kg/m^2	Gould et al., 2014
Puntos de corte para definir reducida función muscular			
Velocidad de la marcha	≤0,8 m/s		Cruz-Jentoft et al., 2010a Studenski et al., 2011
SPPB	≤8 puntos		Pavasini et al., 2016 Guralnik et al., 1995
TUG	≥20 s		Bischoff et al., 2003
Test del camino de 400 m	No completarlo o ≥6 min para completarlo		Newman et al., 2006

ASM: *Appendicular Skeletal Mass*; m: metros; s: segundos; SPPB: *Short Physical Performance Battery*; TUG: *Test Up and Go*

El diagnóstico de sarcopenia se realiza en aquellos casos en los que tras el primer cribado, se observa una masa muscular reducida y además se utiliza el tercer criterio de capacidad funcional para identificar la severidad de la misma. El avance de la investigación en sarcopenia y la importancia clínica demostrada han conducido a la Organización Mundial de la Salud (OMS) a reconocer la sarcopenia como un síndrome geriátrico, asignándole desde el 2016 un código propio (M62.84) en el ICD-10-CM (*International Classification Disease - 10 revision - Clinical Modification)* (Cao y Morley, 2016).

1.2 Prevalencia

La prevalencia de sarcopenia aumenta con la edad y varía en los varones y mujeres (Shafiee et al., 2017). Con el crecimiento de la población previsto para Europa para los próximos decenios, se prevé que el número de sujetos con sarcopenia pueda crecer pudiendo pasar del 11,1% estimado en 2016 hasta el 12,9% en 2045 (Figura 4) (Ethgen et al., 2017).

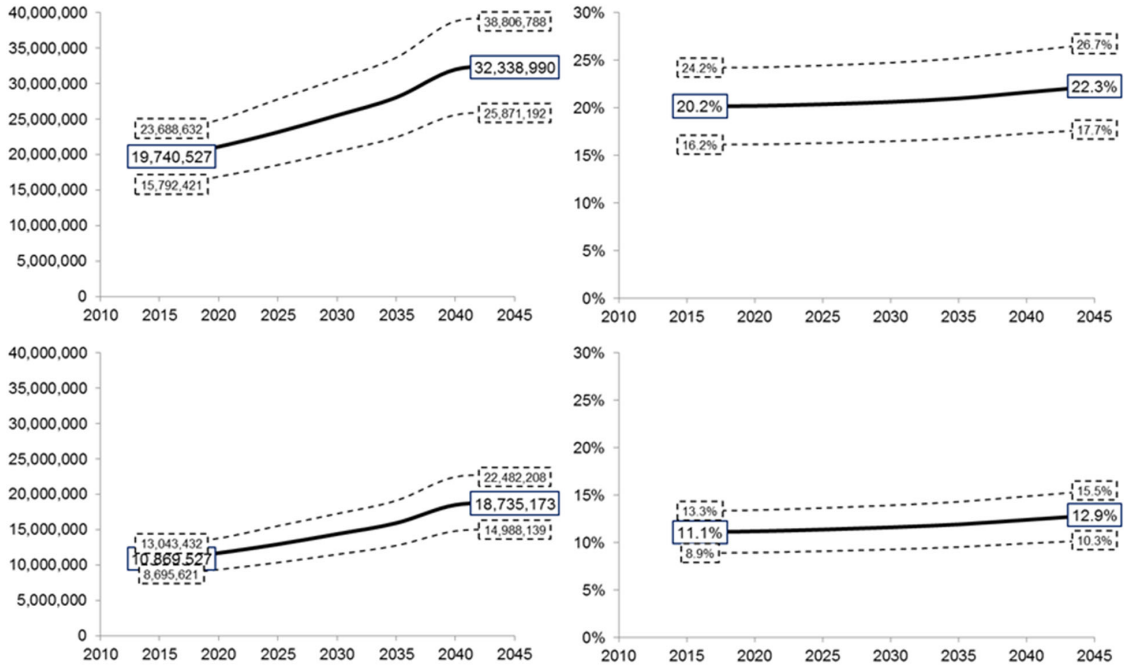

Figura 4. Previsión del aumento de la prevalencia de sarcopenia en Europa desde 2016 al 2045 (en los recuadros izquierdos se presentan los números de casos, y el porcentajes a la derecha), según las estimaciones mayores (recuadros superiores) o menores (recuadros inferiores). Las líneas discontinuas representan ±20% del análisis de sensibilidad (Ethgen et al., 2017).

La prevalencia de sarcopenia varía dependiendo del ámbito de reclutamiento de los sujetos (comunidad, residencias, hospitales de agudos o rehabilitación), y en base a los criterios diagnósticos utilizados (Beaudart et al., 2015). En las personas mayores de la comunidad, la prevalencia de sarcopenia es de alrededor del 10%, con una amplia heterogeneidad entre el 1 y el 29% (Cruz-Jentoft et al., 2014; Shafiee et al., 2017). Otro factor que influye sobre la variabilidad en la prevalencia de sarcopenia es la definición utilizada para diagnosticar la misma. Mayhew y colaboradores (2019) han observado que para los sujetos de la comunidad utilizar los criterios del EWGSOP se asocia

con menor prevalencia, y sobre todo con menor variabilidad siendo la prevalencia del 12,9% (entre el 9,9% y el 15,9%) (Mayhew et al., 2019). En una reciente revisión sistemática en la que se incluyeron estudios realizados en residencias utilizando los criterios del EWGSOP, los autores encontraron una prevalencia de sarcopenia del 41% (entre el 29 y el 73%) (Shen et al., 2019). En los pacientes mayores ingresados en hospitales de agudos se calcula una prevalencia de sarcopenia de casi el 16% (12,4% en mujeres, y 23,5% en varones) (Perna et al., 2017), mientras que en unidades de rehabilitación post agudos la prevalencia sube hasta el 56% (entre el 28 y el 69% dependiendo de los estudios) (Churilov et al., 2018).

Los puntos de corte utilizados para la masa muscular, la fuerza de prensión de la mano y la velocidad de la marcha, son factores muy importantes a tener en cuenta para la estimación de la prevalencia de sarcopenia. Masanés y colaboradores (2017) han demostrado en un estudio transversal que los diferentes puntos de corte para definir la masa muscular normal o reducida son los que más hacen modificar la prevalencia de sarcopenia en personas mayores atendidas en consulta o que viven en residencia, mientras que modificar los puntos de corte para la velocidad de la marcha o para la fuerza de prensión de la mano tiene un impacto menor (Masanés et al., 2017).

1.3 Complicaciones

La sarcopenia se asocia con eventos adversos de salud, siendo muy importante identificarla y realizar un diagnóstico precoz. La sarcopenia en general, y los parámetros que componen su algoritmo de diagnóstico, son importantes factores de riesgo para el desarrollo de alteraciones de la movilidad y discapacidad física. Cesari y colaboradores (2014) analizando los resultados del estudio longitudinal *"invecchiare in Chianti"* en personas mayores de la comunidad tras 9 años de seguimiento observaron que la velocidad de la marcha se asociaba con el desarrollo de discapacidad en las actividades básicas de la vida diaria (Cesari et al., 2014). En la misma línea estudios posteriores observaron resultados superponibles en poblaciones diferentes (Hirani et al., 2015; Tang et al., 2018; Uemura et al., 2019).

Las complicaciones más temidas de la mala salud muscular son las caídas y las fracturas. Los resultados de un estudio longitudinal han

demostrado que la sarcopenia, y en especial la disminución de la fuerza de prensión de la mano se asocia con caídas de repetición (Schaap et al., 2018).
La sarcopenia comparte mecanismos fisiopatológicos con la osteoporosis, dando lugar a un "nuevo" síndrome geriátrico definido como "osteosarcopenia" (Di Monaco et al., 2018; Hirschfeld et al., 2017), el cual se asocia con masa magra y densidad mineral ósea reducidas. La presencia de osteosarcopenia se asocia con mayor incidencia de caídas y fracturas en varones (Scott et al., 2018).

La fractura de cadera es un importante problema sanitario, por sus altos costes económicos sobre los sistemas de salud (Leal et al., 2016), así como por sus importantes consecuencias sobre el estado de salud, la autonomía y la calidad de vida de las personas que la sufren (Veronese y Maggi, 2018). La incidencia de fracturas de cadera aumenta con la edad, y en España se calcula que en mujeres de edad ≥ 85 años la incidencia es de 2.363 casos cada 100.000, y en varones de la misma edad es de 1.312 casos por 100.000 habitantes (Azagra et al., 2014). Las estrategias que consigan reducir la incidencia de caídas muy probablemente son eficaces en prevenir las fracturas de cadera, y por lo tanto representan importantes objetivos de mejora de la asistencia de las personas mayores (Pérez-Ros et al., 2016).

Una de las consecuencias más temidas de las fracturas de cadera es la pérdida funcional, ya que se ha observado que los sujetos que sufren una fractura de cadera con frecuencia no recuperan su estado funcional previo a la fractura (Uriz-Otano et al., 2015). Las complicaciones post-quirúrgicas, como el síndrome confusional agudo entre otros, influyen sobre la pérdida funcional, y la evidencia actual apunta a que la malnutrición (definida con el *Mini Nutritional Assessment*, MNA) se asocia con aumento de la prevalencia de síndrome confusional agudo (Mazzola et al., 2017). Además, la malnutrición ha demostrado ser un factor de riesgo para estancias hospitalarias más largas, y se asocia con una peor recuperación funcional (Inoue et al., 2017).

La sarcopenia es el factor de riesgo más importante para las caídas, y estas son los principales determinantes de las mismas fracturas (Lázaro-del Nogal et al., 2008). Un problema importante que hay que tener en cuenta es que el estilo de vida sedentario, y aún más el encamamiento, son importantes factores asociados a la atrofia muscular (Gianoudis et al., 2015; Shad et al.,

2016). De hecho, pocos días (5-6 días) de encamamiento relativo se asocian con importantes pérdidas de masa muscular en las personas mayores (Kouw et al., 2018).

Varios estudios han demostrado una prevalencia elevada de sarcopenia en personas mayores con fractura de cadera, observando además una significativa asociación entre sarcopenia y recuperación parcial tras la fractura, tanto en unidades de rehabilitación (Landi et al., 2017) como en hospitales de agudos (González-Montalvo et al., 2016; Steihaug et al., 2018).

1.4 Tratamiento

La sarcopenia es considerada un síndrome tratable y reversible. Las bases del tratamiento de la sarcopenia incluyen dos posibles enfoques: identificar los individuos de riesgo, e instaurar medidas de estilos de vida saludable. En los últimos decenios ha mejorado el conocimiento sobre la biología molecular del músculo, lo que puede representar un importante objetivo del tratamiento para el futuro (Morley et al., 2014). Actualmente las bases del tratamiento de la sarcopenia se fundamentan en el ejercicio físico y la suplementación nutricional (Morley, 2016; Rizzoli, 2015).

En relación al ejercicio físico, podemos diferenciar 4 tipos de entrenamientos (Montero-Fernández y Serra-Rexach, 2013): 1) ejercicio aeróbico (correr, nadar, andar en bici); 2) de resistencia; 3) de flexibilidad (estático, dinámico o activo); y 4) de equilibrio (estático o dinámico).

Las bases de la importancia de la actividad física para una buena salud muscular se fundamentan sobre la demostrada evidencia de que la pérdida muscular asociada a la edad es menor en sujetos mayores que han realizado actividad física regular durante su vida, respecto a sujetos sedentarios (Zampieri et al., 2015). Además, la estructura microscópica del músculo (fibras tipo I y II, isoforma beta de la troponina, cadenas ligeras de miosina de tipo lento), de las personas mayores entrenadas es superponible a la de los jóvenes (Klitgaard et al., 1990). El ejercicio de resistencia es el que más se asocia con mejora del rendimiento muscular, así como con la reducción de eventos adversos (como caídas) (Cadore et al., 2014; Valenzuela, 2012). Los beneficios del ejercicio físico mejoran con la suplementación nutricional en sujetos con déficits nutricionales (Denison et al., 2015).

Para la salud muscular de las personas mayores tiene un papel muy importante la vitamina D (Ribera Casado, 2012). La vitamina D tiene dos posibles orígenes: 1) cutáneo y 2) dietético. El 7-dehidrocolesterol, es convertido a nivel cutáneo en vitamina D_3 por efecto de la absorción de la energía solar (Wacker y Holick, 2013). Una pequeña proporción de vitamina D se ingiere con la dieta. La vitamina D_2 (Ergocalciferol) procede de los vegetales y la vitamina D_3 (Colecalciferol) de los productos frescos de origen animal, así como del salmón o atún en conserva, y del aceite de hígado de bacalao (Munns et al., 2016). Diversos mecanismos han sido propuestos como mediadores de los efectos de la vitamina D sobre la fuerza, función y metabolismo muscular, incluidos cambios en la síntesis de proteínas, la miogénesis, la actividad mitocondrial, la regeneración muscular así como el metabolismo de la glucosa (Montenegro et al., 2019). A pesar de esto, sigue pendiente de dilucidar el mecanismo exacto de regulación a nivel muscular y cómo trasladar esto a nivel terapéutico. La hipótesis más verosímil parece ser la mediación del receptor para la vitamina D (Bischoff-Ferrari, 2012). El número de receptores para la vitamina D presentes a nivel muscular se reduce con la edad, pero hay evidencia de que la expresión de este receptor puede cambiar con la suplementación de vitamina D (Pojednic et al., 2014). La suplementación de vitamina D ha demostrado aumentar las fibras musculares de tipo IIa (Knutsen et al., 2010), así como importantes beneficios en la reducción del riesgo de caídas (Bolland et al., 2014).

En relación al tratamiento nutricional, en las personas mayores se observa una reducción de la ingesta asociada a múltiples factores que puede condicionar el desarrollo de malnutrición (Malafarina et al., 2013a). La malnutrición es muy prevalente en las personas mayores y la importante relación entre estado nutricional y salud muscular se pone de manifiesto tras la inclusión de la “masa muscular reducida” como criterio de malnutrición (Landi et al., 2018). Varias sociedades de nutrición (la europea ESPEN, *European Society of Enteral and Parenteral Nutrition*, la americana ASPEN, *American Society of Enteral and Parenteral Nutrition*, la asiática PENSA, *the Parenteral and Enteral Nutrition Society of Asia,* y la latinoamericana FELANPE, Federación Latinoamericana de Terapia Nutricional, Nutrición Clínica y

Metabolismo) han acordado definir la malnutrición incluyendo entre los criterios fenotípicos la masa muscular reducida (Figura 5) (Cederholm et al., 2019).

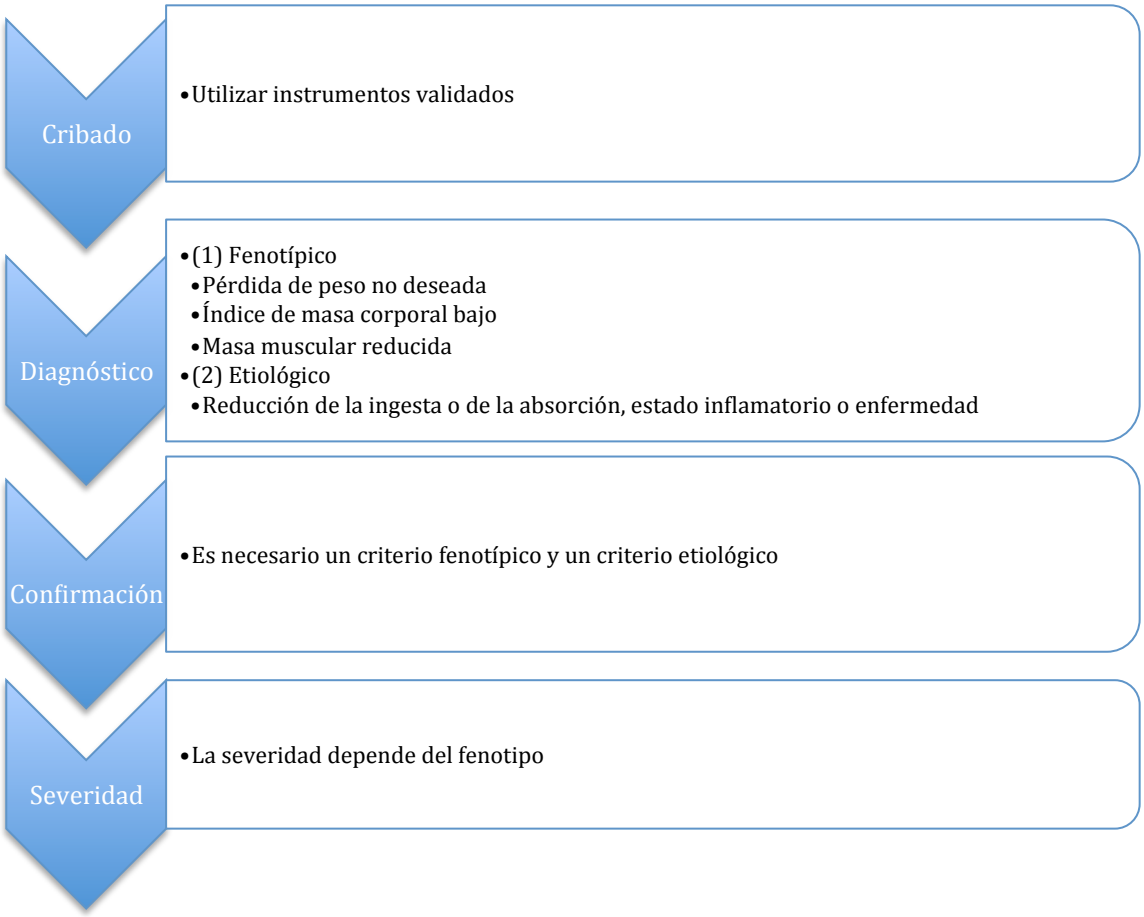

Figura 5. Esquema diagnóstico de malnutrición propuesto por *Global Leadership Initiative on Malnutrition*, GLIM (Cederholm et al., 2019).

En las personas sanas, la síntesis y degradación de las proteínas están en equilibrio, pero en presencia de estímulos hipercatabólicos (como la inflamación o patologías agudas) la degradación de las proteínas aumenta con el resultado del excesivo catabolismo de los aminoácidos (Pasini et al., 2018). La homeostasis muscular se ve condicionada por un factor conocido como "resistencia anabólica" que se observa en las personas mayores y que podría limitar la utilización de los nutrientes de la dieta. Esta resistencia mejora aumentando el aporte proteico, por ejemplo con suplementación nutricional (Wilkinson et al., 2018). La suplementación nutricional ha demostrado beneficios en el tratamiento de la sarcopenia en diferentes ámbitos de salud

(Granic et al., 2019; Isanejad et al., 2016; Malafarina et al., 2013c; Morley, 2015; Robinson et al., 2018; Veronese et al., 2019; Yoshimura et al., 2016), incluido en ancianos con demencia que viven en residencia (Gil Gregorio et al., 2003; Ribera Casado, 2002). En las personas mayores resulta fundamental una adecuación de la dieta (Clegg y Williams, 2018), sobre todo dirigida a vigilar que la ingesta proteica sea adecuada a las recomendaciones actuales de 1-1,2 g/kg/d en las personas mayores sanas, incrementándose hasta 1,2-1,5 g/kg/d para los pacientes con patologías agudas o crónicas (Bauer et al., 2013).

El músculo de las personas mayores es menos sensible al estímulo anabólico de las proteínas que el músculo de las personas jóvenes, por este motivo además de la cantidad es muy importante la calidad de la dieta (Boirie, 2013). Los aminoácidos de cadera ramificada, como la leucina, han demostrado ser capaces de estimular la síntesis proteica, pero para alcanzar la cantidad que ha demostrado esta actividad metabólica (2,5-2,8 g de leucina) es necesaria la suplementación nutricional (Bauer et al., 2015).

En los últimos años ha crecido mucho la evidencia de los beneficios del β-hidroxi-β-metil-butirato (HMB), metabolito activo de la leucina (Rossi et al., 2017). Se ha demostrado que el HMB reduce la degradación de proteínas, regula la síntesis de proteínas y aumenta la producción de colesterol de las células musculares, lo que conduce a membranas celulares más estables (Eley et al., 2008, 2007; Hickson, 2015). Se afirma que la suplementación con HMB ejerce efectos positivos tanto en condiciones saludables (es decir, aumentar el rendimiento deportivo y reducir el daño muscular relacionado con el ejercicio) como patológicas (es decir, preservar y aumentar la masa muscular) tal vez al reducir la degradación de proteínas y mejorar la síntesis de proteínas (Molfino et al., 2013; Zanchi et al., 2011). Aunque el HMB se puede sintetizar endógenamente a partir de leucina, se necesitaría consumir aproximadamente 60 g de leucina diariamente para alcanzar la dosis de HMB de 3 g/día que se ha utilizado en la mayoría de los estudios anteriores (Wilson et al., 2008). Las fuentes de proteínas con alto contenido de leucina, como lácteos, huevos y carnes, contienen aproximadamente del 7% al 10% de leucina (Fitschen et al., 2013). Por lo tanto, para obtener 60 g de leucina de la dieta, uno debería consumir al menos 600 g de proteína de una fuente de proteína alta en leucina

diariamente. Claramente, este nivel de consumo no es práctico; por lo tanto, para obtener HMB 3 g/día, es necesaria la suplementación de HMB. El equilibrio neto de proteínas es positivo durante el crecimiento cuando la síntesis de proteínas excede la degradación, mientras que el equilibrio neto es negativo durante la pérdida de peso, el envejecimiento y en poblaciones clínicas cuando la degradación excede la síntesis (Fitschen et al., 2013). La capacidad de regeneración muscular se ve afectada en los ancianos, pero cuando los mioblastos se incubaron con HMB, aumentaron las expresiones del factor regulador miogénico D y la miogenina, lo que sugiere que el HMB puede aumentar la activación de las células satélite y aumentar la capacidad de regeneración muscular (Kornasio et al., 2009).

Varios estudios han valorado los beneficios de la suplementación nutricional de 3 g/día de HMB, demostrando un aumento de la masa muscular (Baier et al., 2009; Kuriyan et al., 2016; Vukovich et al., 2001). La suplementación nutricional enriquecida en HMB ha mostrado beneficios tanto en personas mayores de la comunidad como en hospitalizadas (Sanz-Paris et al., 2018).

Adicionalmente al tratamiento habitual existen otras líneas de investigación para el abordaje de la sarcopenia (Tabla 3). Desde hace algunos años la investigación para desarrollar tratamientos para la sarcopenia se está centrando sobre los componentes anabólicos e inhibidores del catabolismo muscular (Dennison et al., 2017).

La testosterona aumenta la masa muscular, pero se asocia con muchos efectos adversos (Travison et al., 2011). Por este motivo se continúa investigando la acción de moduladores selectivos de los receptores de los andrógenos (Dalton et al., 2011; Papanicolaou et al., 2013).

Tabla 3. Estrategias actuales de investigación farmacológica para el tratamiento de la sarcopenia (Dennison et al., 2017).

Objetivo	Compuesto	Mecanismo de acción	Nivel de evidencia
Receptor de los andrógenos	Testosterona	Promueve la hipertrofia de las fibras musculares activando los receptores androgénicos	Estudios en fase II
Receptores de los andrógenos	Moduladores selectivos de los receptores de los andrógenos (ejemplos: Embosarm y MK-0773)	Promueve la hipertrofia de las fibras musculares activando los receptores androgénicos	Estudios en fase II
Miostatina	Anticuerpo monoclonal de la miostatina (Bimagrumab)	Promueve la hipertrofia de las fibras musculares bloqueando la miostatina	Estudios de fase II
Receptor de la activina tipo IIB (ACTRIIB)	Segmento soluble de la proteína ACTRIIB-Fc (sACTRIIB-Fc)	Promueve la hipertrofia muscular mediante el bloqueo del receptor ACTRIIB	Estudios en animales

La miostatina es un inhibidor del crecimiento muscular, por lo que se están investigando anticuerpos monoclonales antimiostatina para intentar prevenir y revertir la pérdida muscular (Becker et al., 2015).

Por último, hay evidencia de la importancia de la disfunción mitocondrial y de su potencial como objetivo del tratamiento (Marzetti et al., 2013), y en un estudio piloto se ha observado esta asociación entre disfunción mitocondrial y sarcopenia en sujetos mayores con fractura de cadera (Marzetti et al., 2016).

1.5 Mortalidad

La sarcopenia se asocia con aumento del riesgo de mortalidad (Arango-Lopera et al., 2013), que llega a ser más de tres veces mayor en personas mayores de la comunidad (Liu et al., 2017), de residencia (Beaudart et al., 2017), y en las personas mayores hospitalizadas (Figura 6) (Sipers et al., 2019; Vetrano et al., 2014; Yang et al., 2017).

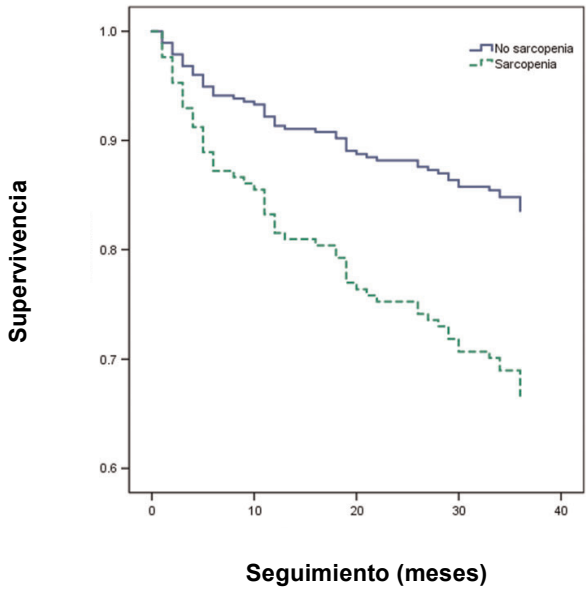

Figura 6. Gráfico de supervivencia en las personas hospitalizadas en base a la presencia de sarcopenia. Test log-rank p<0,001. (Yang et al., 2017).

La presencia de sarcopenia, además, se asocia con el desarrollo de discapacidad en las actividades básicas de la vida diaria, con institucionalización y mortalidad tanto en varones (Hirani et al., 2015), como en mujeres (Sim et al., 2019). La pérdida funcional es uno de los factores asociados a la institucionalización tras una fractura de cadera (Uriz-Otano et al., 2016), y con la mortalidad a 3 años (Daniel D Bohl et al., 2017). La hipoalbuminemia es un importante marcador del estado nutricional y se asocia con aumento del riesgo de muerte en personas mayores con fractura de cadera (Daniel D Bohl et al., 2017; Cabrerizo et al., 2015). La malnutrición definida con el MNA también ha demostrado aumentar el riesgo de muerte en las personas mayores con fractura de cadera (Goisser et al., 2015; Helminen et al., 2017).

2 HIPÓTESIS Y OBJETIVOS

2.1 Hipótesis

En las personas mayores el encamamiento asociado a la hospitalización y la reducida movilidad tras una fractura de cadera se asocian con pérdida de peso y de masa muscular.

La hipótesis de este proyecto de investigación es que el estado nutricional y la salud muscular influyen sobre la recuperación tras una fractura de cadera y sobre la mortalidad. En este sentido, se espera que el tratamiento rehabilitador asociado a la suplementación nutricional mejore la recuperación funcional y la situación de desnutrición en los pacientes mayores con fractura de cadera.

2.2 Objetivo general

El objetivo de esta investigación es evidenciar el estado nutricional de las personas mayores con fractura de cadera y valorar cómo influyen la suplementación nutricional y la rehabilitación física sobre la recuperación funcional y sobre el estado nutricional. Las actuaciones estarán encaminadas a evaluar la salud muscular (sarcopenia) y su impacto sobre la evolución funcional y la mortalidad en estos pacientes.

2.3 Objetivos específicos

Los objetivos específicos de este proyecto de investigación son.

1. Exponer cómo la desnutrición y la intervención nutricional influyen sobre la evolución clínica y la mortalidad en las personas mayores con fractura de cadera (Capítulo 1).
2. Valorar si la suplementación nutricional oral enriquecida en HMB y VitD, mejora la masa muscular y marcadores del estado nutricional (IMC y proteínas plasmáticas totales) en los pacientes mayores con fractura de cadera (Capítulo 2).
3. Identificar los factores asociados con la presencia de sarcopenia al ingreso (sarcopenia crónica) y con el desarrollo de sarcopenia durante la estancia hospitalaria (sarcopenia incidente) en pacientes de edad avanzada con fractura de cadera, e investigar la influencia de la sarcopenia sobre el riesgo de mortalidad durante 7 años de seguimiento (Capítulo 3).

3 SUJETOS Y MÉTODOS

A continuación se muestra la metodología utilizada para alcanzar los objetivos específicos planteados (Figura 7). Se ha realizado una revisión de la literatura, y se han estudiado dos poblaciones: (1) estudio HIPERPROT-GER (intervención hiperproteica en pacientes con fractura de cadera) y (2) estudio PREFISSARC-GER (PREvalencia y FISiopatología de la SARCopenia en pacientes con fractura de cadera)

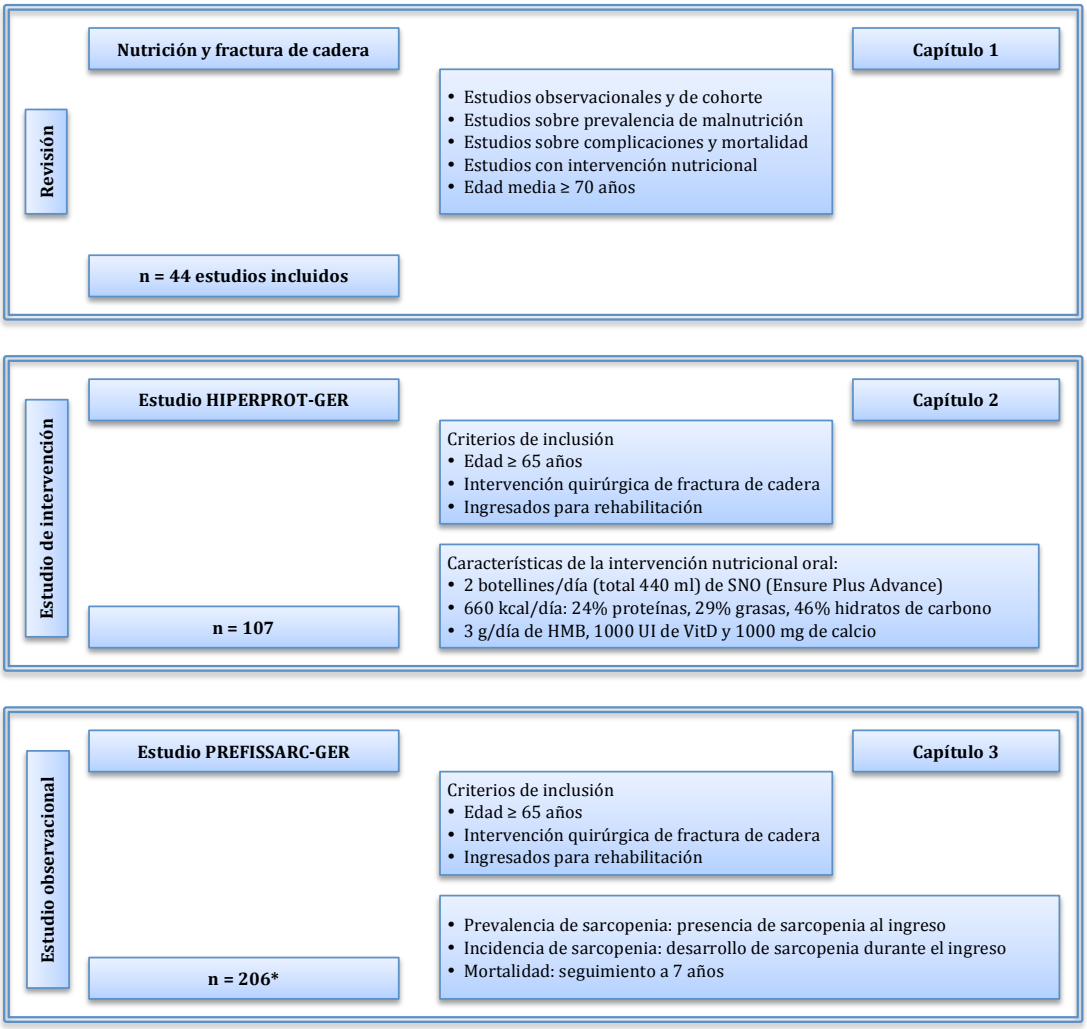

Figura 7. Diseño, tamaño de la muestra y criterios de inclusión de los estudios realizados.
* la muestra engloba los 107 sujetos incluidos en el estudio HIPERPROT.

HIPERPROT-GER, intervención HIPERPROTeica en GERiatría; PREFISSARC-GER, PREValencia y FISiopatología de la SARCopenia en GERiatría.

3.1 Estado nutricional, nutrición y fractura de cadera. Revisión.

3.1.1 Estrategia de búsqueda

La búsqueda se llevó a cabo mediante la base de datos MEDLINE, considerando los artículos publicados hasta diciembre de 2017. Como palabras claves se utilizaron las siguientes: "*older adults/people, elderly, hip fracture/femur, nutrition, nutritional status/biomarkers/intervention/screening tool, risk of malnutrition, diagnosis of malnutrition, albumin/protein, under-nutrition, body mass index, supplement/supplementation, results, outcomes, effects, pressure ulcers, complication, and mortality".* La búsqueda se limitó a los artículos que contenían las palabras claves bien en el título o en el resumen, en inglés, español o italiano.

3.1.2 Criterios de inclusión

Se incluyeron estudios que valorasen el estado nutricional en los pacientes con fractura de cadera y su relación con las complicaciones, la evolución clínica y funcional, y la mortalidad. Además, de estudios que evaluasen los efectos de la intervención nutricional. Fueron excluidas las revisiones y los protocolos que no arrojaban resultados.

3.1.3 Obtención de datos

El título y el resumen de los artículos resultado de la búsqueda fueron evaluados por dos investigadores que realizaron la extracción de los datos. Las dudas fueron discutidas y en el caso de no poder solucionarlas se pidió la opinión de un tercer revisor. Se agruparon los estudios en base al objetivo principal.

3.2 Estudio HIPERPROT-GER

3.2.1 Diseño del estudio y participantes

Hyperprotein Nutritional Intervention in Elderly Patients with Hip Fracture and Sarcopenia (HIPERPROT-GER) *study*, es un estudio multicéntrico, aleatorizado controlado, de diseño abierto. Durante los 4 años de estudio (enero del 2012 hasta diciembre 2015) se incluyeron de forma prospectiva a todos los pacientes de edad igual o mayor de 65 años con diagnóstico de fractura de cadera de bajo impacto (por caída), ingresados en las unidades de rehabilitación post agudos del Hospital San Juan de Dios de Pamplona (2012 y 2013) y del Hospital Viamed Valvanera de Logroño (2014 y 2015). Fueron excluidos los pacientes con diabetes, con índice de Barthel < 40 antes de la fractura, tumor en tratamiento con quimioterapia o radioterapia, con fractura patológica o de alto impacto (accidente de trafico) (Tabla 4).

Tabla 4. Criterios de inclusión y exclusión.

Inclusión	Exclusión
• Edad ≥ 65 años • Intervenidos quirúrgicamente de fractura traumática de cadera(1) • Ingresados para rehabilitación	• Índice de Barthel previo al ingreso < 40 • Desnutrición: IMC < 21 kg/m^2 y/o MNA < 11 y/o albúmina < 2,1 g/dL • Obesidad mórbida: IMC > 40 kg/m^2 • Diabetes mellitus • Disfagia para líquidos • Fractura patológica de cadera o enfermedad oncológica en fase activa o que estén recibiendo tratamiento (radioterápico o quimioterapico) • Condiciones clínicas graves que comprometan y pongan en riesgo la vida del paciente o índice de Charlson ≥ 6

(1) Se considera traumática la fractura derivada de una caída accidental, definiendo caída cualquier acto inesperado que determina que el paciente llegue a un nivel más bajo de donde se encontraba originariamente. IMC: índice de masa corporal; MNA: *Mini-Mutritional Assessment*.

De un total de 205 pacientes con fractura de cadera ingresados durante el periodo de estudio, 107 se incluyeron en el estudio. El estudio cumple con las líneas guías CONSORT para los ensayos aleatorizados (Moher et al., 2010). El protocolo del estudio ha sido registrado en el registro nacional norte

americano (*National Institute of Health*, NIH) en la página: www.clinicaltrials.gov, con el código NCT01404195, registrado el 22 de Julio de 2011 (Malafarina et al., 2013b).

El estudio fue aprobado por el Comité Ético de Investigación Clínica de la Comunidad Foral de Navarra (62/2011), y preparado en conformidad con los requisitos de la Buena Práctica Clínica de la Unión Europea (EU, 1996) y la revisión actual de la Declaración de Helsinki (WMA, 1964). El consentimiento informado, fue firmado por todos los pacientes o por sus representantes legales, y se les informó de que podían abandonar el estudio en cada momento sin repercusiones negativas.

3.2.2 Descripción de las unidades de rehabilitación

En Navarra se registran alrededor de 600 fracturas de cadera al año, y casi 300 en la Rioja (Alvarez-Nebreda et al., 2008). De estas, casi un tercio, tras la intervención quirúrgica son derivadas a las unidades de rehabilitación post-agudos del Hospital San Juan de Dios (Pamplona) y Hospital Viamed Valvanera (Logroño). Los motivos de derivación son la alta complejidad clínica (definida en función de la alta comorbilidad y de la presencia de complicaciones durante el ingreso), o la respuesta parcial al tratamiento rehabilitador realizado en la unidad de traumatología.

3.2.3 Grupos del estudio

Los sujetos incluidos fueron aleatorizados a grupo de intervención (GI) recibiendo la dieta del hospital más suplemento nutricional oral, o a grupo de control (GC) recibiendo únicamente la dieta del hospital. Los pacientes en el GI recibieron dos botellines al día (uno por la mañana y uno por la tarde) de suplemento nutricional líquido, ya preparado (220 ml x 2, 660 Kcal totales) (Ensure® Plus Advance, Abbott Laboratorios S.A.), cuyas características nutricionales son: 1,5 Kcal/ml, 24% de origen proteico (9,1 g/100 ml), 29% grasa (5 g/100 ml), 46% hidratos de carbono (16,8 g/100 ml). El suplemento está enriquecido con HMB 0,7 g/100 ml, Vit-D 227 UI/100 ml y calcio 227 mg/100 ml.

3.2.4 Estudio de la sarcopenia

El test para calcular la velocidad de la marcha fue realizado por una fisioterapeuta debidamente formada, sobre la distancia de 4 metros. Se considera velocidad de la marcha reducida valores ≤0,8 m/s (Cruz-Jentoft et al., 2010a). La fuerza fue medida (fisioterapeuta) en las dos manos utilizando un dinamómetro digital tipo JAMAR (Akern, Italia), según el protocolo original,[28] repitiendo la medición dos veces, tras 60 segundos de descanso. Se registró el resultado mayor. La fuerza se consideró reducida para valores obtenidos en mujeres < 20 kg, y en varones < 30 kg (Cruz-Jentoft et al., 2010a).

El análisis de la composición corporal se llevó a cabo mediante análisis por bioimpedanciometría (BIA) utilizando el equipo BIA-101 (Akern, Italia). La medida se evaluó con el paciente en posición supina, sobre una superficie no conductora, con las extremidades superiores ligeramente abducidas del tronco y las extremidades inferiores ligeramente separadas, posicionando los electrodos en el lado no afectado por la fractura. La masa muscular esquelética (SMM) se calculó con la siguiente fórmula (Janssen et al., 2000):
SMM (kg)=[(talla^2/BIA-resistencia x 0,401) + (sexo x 3,825) + (edad x -0,071)] + 5,102.

Se midió la talla en cm; BIA-resistencia en Ohmios; el sexo varón=1 y mujer=0; y la edad en años. Además, se calculó en Índice de Masa Muscular Esquelético (SMI): SMI (kg/m^2) = SMM/ talla en m^2 (Janssen et al., 2004a). Definiendo en varones SMI normal > 10,75, sarcopenia moderada, entre 10,75 y 8,51, y sarcopenia severa <8,51 kg/m^2, y en mujeres > 6,75, entre 6,75 y 5,76, y <5,76 kg/m^2, respectivamente. La sarcopenia se definió según los criterios propuestos por el EWGSOP (Cruz-Jentoft et al., 2010a).

3.2.5 Variables antropométricas y clínicas

El peso se midió en kg, pesando el paciente en silla de ruedas. La talla (cm) se midió con el paciente en posición supina y se calculó el índice de masa corporal (IMC): peso (kg) / talla (m^2).

El cribado nutricional se llevó a cabo por una nutricionista, utilizando la versión corta del cuestionario validado *Mini Nutritional Assessment-Short Form* (MNA-SF), según la clasificación original: 12-14 puntos bien nutridos, 8-11 riesgo de malnutrición, y 0-7 malnutridos (Kaiser et al., 2009; Rubenstein et al., 2001). El MNA es una herramienta validada de cribado y valoración de malnutrición, y riesgo de malnutrición en el paciente mayor (Guigoz et al., 2002). Se ha utilizado en ancianos institucionalizados y de la comunidad, en pacientes psicogeriátricos y en el entorno hospitalario (Bleda et al., 2002; Cuervo et al., 2009, 2008). Se correlaciona claramente con los parámetros antropométricos y bioquímicos más utilizados, y ha demostrado ser eficaz para predecir el pronóstico en pacientes hospitalizados, así como para valorar cambios en el estado nutricional (Acosta Escribano et al., 2005).

Para la valoración de las actividades básicas de la vida diaria (ABVD), una fisioterapeuta, debidamente formada, utilizó el índice de Barthel (Mahoney y Barthel, 1965) registrando el valor previo a la fractura (entrevista retrospectiva), y al alta. En 1965 Mahoney y Barthel publicaron el índice de Barthel tras 10 años de experiencia valorando pacientes con patología neuromuscular y músculo esquelética ingresados en Maryland (Mahoney y Barthel, 1965). Consta de 10 parámetros: alimentación, baño, vestido, aseo personal, continencia urinaria y fecal, uso de retrete, traslado sillón cama, deambulación y escaleras. El índice de Barthel asume valores entre cero (totalmente dependiente) y cien (completamente independiente). Entre sus ventajas destaca que es una escala sencilla y rápida de realizar, con gran fiabilidad bien por observación directa o por la información obtenida del cuidador, y sensible a cambios. Es numérica, ayudando al manejo estadístico. Además permite estudiar y analizar no solo la puntuación global sino cada una de las actividades y por último introduce mayor número de parámetros de movilidad (traslado cama- sillón, deambulación, escaleras) que en otras escalas, siendo un instrumento de gran utilidad en centros de rehabilitación (Applegate et al., 1990). Los pacientes fueron categorizados según la puntuación del índice de Barthel (BI), en 4 grupos funcionales: dependencia

total por BI < 20, dependencia severa 20-35, dependencia moderada 40-55, e independientes BI > 60 (Uriz-Otano et al., 2015).

La autonomía en la marcha se midió por la fisioterapeuta con la escala de categorías funcional de la marcha (*Functional Ambulation Category* - FAC) (Viosca et al., 2005). Esta escala se empezó a utilizar en los años 80 en el *Massachusetts General Hospital* para evaluar la deambulación de pacientes con enfermedad neurológica (Viosca et al., 2005). Es una escala que clasifica a los pacientes en 6 categorías: 0 = deambulación no funcional o nula; 1 = marcha con gran ayuda física de otra persona; 2 = marcha con ligero contacto manual de otra persona; 3 = marcha con necesidad de supervisión sin contacto físico; 4 = marcha independiente en superficie llana y, por último, 5 = marcha independiente en llano y escaleras. Puede aplicarse mediante observación directa o mediante anamnesis.

Para el estudio cognitivo se utilizó el *Mini Mental State Examination* (MMSE) (Folstein et al., 1975). El MMSE es un test de cribado. Una puntuación baja indica que puede existir un deterioro cognitivo, el cual puede ser una manifestación de diversas enfermedades o síndromes (demencia, delirium etc.). El MMSE consta de 11 ítems relativos a los siguientes dominios: orientación temporo-espacial, memoria inmediata y diferida, atención y cálculo, lenguaje y capacidad visuo-constructiva. Su cumplimentación requiere alrededor de 10 minutos, y se obtiene una puntuación máxima de 30 puntos, con un punto de corte de 24 puntos.

La comorbilidad fue definida en acuerdo al índice de Charlson (Charlson et al., 1987). El índice de Charlson, diseñado originalmente para predecir la mortalidad, es el índice de comorbilidad más empleado tanto en estudios nacionales como internacionales, y está traducido al español (Charlson et al., 1994, 1987). El índice asigna a cada uno de los procesos patológicos un determinado peso (puntuación de 1 a 6) en función del riesgo relativo de muerte que se transforma en una puntuación global. En el artículo original, los sujetos con un índice de 0 tuvieron una mortalidad a los 10 años del 8% frente al 59% de aquellos con una puntuación igual o mayor a 3. En general se

considera ausencia de comorbilidad: 0-1 puntos, baja comorbilidad 2-3 y alta comorbilidad >3.

3.2.6 Valoración analítica y de laboratorio.

El análisis de sangre incluyó hemograma y función renal, proteínas totales, albúmina, transtiretina y 25(OH)D. Para el metabolismo lipídico se midieron la concentración de colesterol total y triglicéridos. Para el estudio del estado inflamatorio se analizaron las concentraciones hemáticas de interleuquina-1 (IL-1), interleuquina-6 (IL-6), y Factor de Necrosis Tumoral-alfa (TNF-α).

Todos los análisis fueron realizados por la mañana tras un ayuno de al menos 8 horas, y repetidos 72 horas antes del alta.

3.2.7 Tratamiento rehabilitador

El tratamiento rehabilitador se realizó de forma igual en los pacientes de los dos grupos, y se compone de dos partes. La primera, desarrollada en la planta de hospitalización (enfermería y auxiliares de enfermería) y se basa en la movilización precoz y marcha con ayudas técnicas (bastón, muleta, o andador). La segunda parte se desarrolla en el gimnasio de los hospitales (fisioterapistas), y consiste en ejercicios de fortalecimiento de la musculatura de las extremidades inferiores, ejercicios de equilibrio y reeducación de la marcha, en sesiones individuales o de grupo, de entre 30 y 45 minutos al día, cinco días a la semana (de lunes a viernes). Los pacientes que no tienen autorizada la carga sobre la extremidad intervenida, empiezan la rehabilitación con ejercicios de fortalecimiento de las extremidades inferiores contra resistencia y con pesa hasta tener autorizada la carga, momento en el que comienzan la rehabilitación de la marcha.

3.2.8 Análisis estadístico

Las variables se presentan como proporción, media ± desviación estándar o mediana y rango interquartílico. Para comparar las medias se

utilizaron los test paramétricos t de Student y F de Fischer-Snedecor, mientras que para comparar los porcentajes se ha utilizado el test χ^2 de Pearson. Para el estudio de las diferencias entre las medias al alta se utilizó el test ANCOVA, corrigiendo el resultado por los valores al ingreso. El análisis estadístico ha sido realizado utilizado el programa *Statistical Package for the Social Sciences* (SPSS), versión 15,0 (SPSS inc., Chicago, IL).

3.3 Estudio PREFISSARC-GER

3.3.1 Diseño del estudio y participantes

Estudio pragmático, observacional prospectivo y multicéntrico. Han sido incluidos de forma prospectiva todos los pacientes mayores de 65 años, ingresados para rehabilitación tras haber sido intervenidos por fractura de cadera.

El protocolo del estudio fue aprobado por el comité de ética local (Comité de Ética de Investigación Clínica de la Comunidad Foral de Navarra) (salida nº33 del 17/2/2012). Todos los sujetos incluidos firmaron el consentimiento informado. El protocolo del estudio ha sido registrado en el registro nacional norte americano (*National Institute of Health*, NIH) a la pagina: www.clinicaltrials.gov con el código NCT 01477086 del 22/11/2011. El estudio ha sido realizado en acuerdo con la Declaración de Helsinki (WMA, 1964).

3.3.2 Descripción de las unidades de rehabilitación

El estudio se llevó a cabo en las unidades de rehabilitación post-agudos de dos hospitales, el Hospital San Juan de Dios de Pamplona (entre Enero 2012 y Agosto 2014), y del Hospital Viamed Valvanera de Logroño (entre Noviembre 2014 y Diciembre 2015). Fueron excluidos los pacientes con fractura patológica o periprotésica, y los paciente con patología oncológica activa o en tratamiento paliativo con esperanza de vida inferior a un año.

La duración del seguimiento se calculó como el intervalo entre la fecha de comienzo del estudio (ingreso en la unidad de rehabilitación) y la fecha de fallecimiento, o la fecha en que finalizó el seguimiento (31 de julio de 2019) , lo que ocurriera primero.

3.3.3 Estudio de la sarcopenia

El estudio de la sarcopenia se realizó, según los criterios del EWGSOP actualizados en 2019 (Cruz-Jentoft et al., 2019).

La valoración de la fuerza de prensión de la mano fue medida con un dinamómetro digital (DynX® Akern, Florencia) según el protocolo estándar (Roberts et al., 2011). La fuerza se midió en las dos manos, registrando el valor mayor de dos pruebas consecutivas con cada mano, considerando fuerza reducida valores <27 kg en varones, y <16 kg en mujeres.

El estudio de la masa muscular se realizó mediante BIA (BIA, Akern, Florencia), obteniendo valores de resistencia (Rz) y reactancia (Xc) en ohms, y calculando el ángulo de fase en grados. La medición ha sido realizada por la mañana, en ayunas, colocando los electrodos (BIA *trodes* de Akern) en el tobillo de la pierna no operada y en la muñeca del mismo lado. El paciente se colocó en posición supina, sobre una superficie no conductora, con los brazos separados del tronco, y las piernas ligeramente separadas, para que no haya contacto entre ellas. La masa muscular esquelética apendicular (ASMM) se calculó de acuerdo a la siguiente formula (Sergi et al., 2015):

ASMM (kg) = -3,964 + (0,227 x RI) + (0,095 x peso) + (1,384 x sexo) + (0,064 x Xc).

Donde RI es el *Resistive Index* calculado como (talla en cm^2/Rz), el peso en kg, asumiendo para el sexo valores de 0 para las mujeres y 1 para los varones. Entre las formulas validadas para el estudio de la composición corporal con BIA en ancianos, la fórmula de Sergi y colaboradores (2015) ha demostrado la mayor sensibilidad y especificidad (Steihaug et al., 2016). El índice de masa muscular esquelético (SMI), corregido por la talla se obtuvo con la fórmula: SMI kg/m^2= ASMM/talla en m^2.

El SMI ha sido definido reducido por valores menores de 7 kg/m^2 en varones y menores de 6 kg/m^2 en mujeres (Cruz-Jentoft et al., 2019). Ambos estudios, el de la composición corporal con BIA y el de la fuerza de prensión de la mano han sido realizados al ingreso y 48 horas antes del alta. La velocidad de la marcha ha sido medida solo al alta, por la imposibilidad de caminar de forma segura al ingreso.

La velocidad de la marcha se evaluó con el test de la marcha de 4 metros, considerando velocidad reducida valores ≤0,8 m/s. Esta medida se ha utilizado como criterio para la evaluación de la gravedad de la sarcopenia.

Aquellos pacientes con baja fuerza de prensión de la mano y bajo SMI fueron definidos como sarcopénicos (Cruz-Jentoft et al., 2019).

3.3.4 Variables antropométricas y clínicas

El peso se midió en kg, pesando el paciente en silla de ruedas. La talla (cm) se midió con el paciente en posición supina y se ha calculado el IMC.

El cribado nutricional se llevó a cabo por una nutricionista, utilizando el MNA-SF, según la clasificación original: 12-14 puntos bien nutridos, 8-11 riesgo de malnutrición, y 0-7 malnutridos (Kaiser et al., 2009).

Para la valoración de las actividades básicas de la vida diaria (ABVD), una fisioterapeuta, debidamente formada, utilizó el índice de Barthel (Mahoney y Barthel, 1965) registrando el valor previo a la fractura (entrevista retrospectiva), y al alta.

La autonomía en la marcha se midió por la fisioterapeuta con la escala FAC (Viosca et al., 2005) y para el estudio cognitivo se utilizó el MMSE (Folstein et al., 1975).

3.3.5 Análisis estadístico

Los pacientes fueron clasificardos en cuatro grupos: sujetos no sarcopénicos al ingreso y al alta (grupo control); sujetos con sarcopenia al ingreso y al alta (grupo de sarcopenia crónica); sujetos sin sarcopenia al ingreso pero que desarrollan sarcopenia durante la estancia hospitalaria (grupo de sarcopenia incidente); y pacientes con sarcopenia al ingreso pero que revierten este estado durante la estancia hospitalaria (grupo de sarcopenia revertida). Las variables se presentan como mediana y rango intercuartil (RIC) con la excepción de las variables categorizadas que se presentan como frecuencias. Las diferencias entre los grupos se evaluaron mediante el análisis de varianza (ANOVA) para variables continuas y la prueba χ^2 de Pearson para variables categóricas. El cambio de variables como el peso, el SMI y la fuerza de prensión de la mano se calcularon por las diferencias entre los valores al alta menos los valores al ingreso. Para investigar los factores asociados con el riesgo de sarcopenia (crónica e incidente) se realizó el análisis de regresión

logística múltiple. La relación entre la sarcopenia y las variables clínicas y funcionales se estimó a partir de modelos de regresión logística múltiple (odds ratios, OR). La sarcopenia (incidente y crónica) se incluyó como variable dependiente, y la edad, el sexo, la duración de la estancia hospitalaria, la capacidad funcional (velocidad de marcha, fuerza de prensión de la mano, índice de Barthel), el rendimiento cognitivo, el MNA-SF, y el IMC como factores independientes.

Para investigar la influencia de la sarcopenia (incidente, crónica y la combinación de los dos tipos), así como variables clínicas y funcionales sobre el riesgo de mortalidad después de 7 años de seguimiento, se realizaron análisis de supervivencia mediante regresión de Cox y de Kaplan-Meier. Todas las variables se ajustaban al supuesto de riesgo proporcional. Los modelos de regresión de Cox se ajustaron por posibles factores de confusión; sexo, edad y centro.

Los valores p <0,05 se consideraron significativos. El análisis estadístico se realizó con los programas SPSS y STATA.

4 RESULTADOS

4.1 CAPÍTULO 1

Nutritional Status and Nutritional Treatment are Related to Outcomes and Mortality in Older Adults with Hip Fracture

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Review

Nutritional Status and Nutritional Treatment Are Related to Outcomes and Mortality in Older Adults with Hip Fracture

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Abstract: Malnutrition is very prevalent in geriatric patients with hip fracture. Nevertheless, its importance is not fully recognized. The objective of this paper is to review the impact of malnutrition and of nutritional treatment upon outcomes and mortality in older people with hip fracture. We searched the PubMed database for studies evaluating nutritional aspects in people aged 70 years and over with hip fracture. The total number of studies included in the review was 44, which analyzed 26,281 subjects (73.5% women, 83.6 ± 7.2 years old). Older people with hip fracture presented an inadequate nutrient intake for their requirements, which caused deterioration in their already compromised nutritional status. The prevalence of malnutrition was approximately 18.7% using the Mini-Nutritional Assessment (MNA) (large or short form) as a diagnostic tool, but the prevalence was greater (45.7%) if different criteria were used (such as Body Mass Index (BMI), weight loss, or albumin concentration). Low scores in anthropometric indices were associated with a higher prevalence of complications during hospitalization and with a worse functional recovery. Despite improvements in the treatment of geriatric patients with hip fracture, mortality was still unacceptably high (30% within 1 year and up to 40% within 3 years). Malnutrition was associated with an increase in mortality. Nutritional intervention was cost effective and was associated with an improvement in nutritional status and a greater functional recovery. To conclude, in older people, the prevention of malnutrition and an early nutritional intervention can improve recovery following a hip fracture.

Keywords: older adults; hip fracture; malnutrition; body mass index; nutritional biomarkers

1. Introduction

Hip fractures represent a significant health risk for older populations because the incidence of fractures increases notably with age [1].

Hip fractures in geriatric patients have a negative impact on functional status and quality of life, and are associated with high mortality [2,3]. Despite the reduction in pre-surgery hospital stay (surgery performed in the first 24 h, or 48 h after admission, is associated with fewer post-operative complications) [4], and improvements in the management of complications, many patients with hip fracture presented functional deterioration [5]. Identifying the risk factors that predict functional loss after a hip fracture could reduce the costs associated with the need for help resulting from loss of autonomy [6] and institutionalization [7], and could also improve the treatment of post-operative complications. The need for help in order to be able to walk within a patient's home, Parkinson's disease, smoking, having suffered delirium in the previous month, having a Body Mass Index (BMI) < 22 kg/m^2, and age are among the independent risk factors for hip fractures [8]. Poor nutritional status, defined by the Mini Nutritional Assessment (MNA), was associated with a higher risk of fracture at any site [9]. Among risk factors for hip fracture as well as functional loss after the fracture, malnutrition represents an area of great interest, principally because it is a modifiable risk factor. The identification of malnutrition is widely accepted as an appropriate procedure, which may help to give patients better care [10]. This review represents an actualization of the evidence previously published on this topic. The novelty of this review is that we included not only studies with nutritional interventions, but also studies that have assessed the nutritional status in older patients with hip fracture.

The principal objective of this review is to describe how both nutritional status, as revealed by malnutrition biomarkers, influences the clinical evolution and mortality of older people with hip fracture, as well as the impact of nutritional intervention. We therefore structured this paper into four chapters concerning subjects with hip fracture: (1) prevalence of malnutrition and nutritional status aspects (including anthropometry, blood biomarkers, and energy intake), (2) influence upon outcomes and complications, (3) mortality, and (4) effects of nutritional intervention.

2. Material and Methods

2.1. Data Sources and Search Strategy

A search was carried out on the electronic database MEDLINE for papers published from January 1990 until December 2017. The search strategy is detailed in Supplementary data. The search was restricted to articles in English, Spanish, or Italian. The references of the selected articles were manually revised in the search for eligible articles. Whenever there were studies with multiple publications about the same population, the study with the largest sample was selected, as long as it respected our inclusion criteria.

2.2. Inclusion and Exclusion Criteria

We included observational and cohort studies that evaluated the presence of malnutrition (defined by MNA, BMI, albumin concentration, or weight loss), and the influence of malnutrition, as revealed by nutritional biomarkers, on functional recovery, post-operative complications, and mortality in hip fracture patients. We considered as nutritional biomarkers: (1) anthropometric parameters, such as BMI, mid-arm circumference, and triceps skinfold; (2) blood concentrations of total proteins, albumin, and micronutrients such as vitamin D and calcium. We also included controlled clinical trials with nutritional intervention. We defined an intervention as cases where patients received supplements (either orally, by tube, or intravenously) or advice on the characteristics of the diet (by a specialized nurse or dietician). We consider studies (which included only males, only females, or both sexes) carried out in populations with an average age of 70 years or above. Reviews and protocols that did not provide results were excluded.

2.3. Data Extraction

The title and abstract of papers compiled from the search were evaluated by two researchers who carried out data extraction. Doubts and queries were discussed and whenever these could not be solved, the opinion of a third reviewer was requested. Studies were grouped according to their main objective. When necessary we contacted the corresponding author to request data that did not appear in the paper.

2.4. Quality Assessment

The quality of the selected studies was determined with both the National Institutes of Health (NIH) Quality Assessment tool for Observational Cohort and Cross-Sectional Studies and the Quality Assessment of Controlled Intervention Studies [11]. These tools have been designed to evaluate internal validity and bias risk for both types of observational and intervention studies, and each consists of 14 evaluation criteria. The criteria for observational studies are: aims of the study, sources of bias, sampling, participation rate, study power, data collection methods, and confounding. The criteria for intervention studies are: objective of the study, population characteristics, sampling, selection criteria, sample size justification, exposure measured, timeframe, categories of exposure, independent variables, exposure over the time, dependent variables, blinded, drop-out, and confounding. The criteria were rated as either yes, no, or "other" (i.e., CD, cannot determine; NA, not applicable; NR, not reported). The overall assessment of the studies were classified as "good", "fair", or "poor".

3. Results

This review included 44 papers, which totaled 26,281 subjects with a mean age 83.6 $\pm$ 7.2 years. The population was mostly female (73.5%). The overall quality of the included studies was rated as fair (Supplementary Tables S1 and S2).

3.1. Prevalence of Malnutrition and Nutritional Status Aspects in Hip Fracture Patients

In all of the studies included, malnutrition was identified by a validated nutritional assessment tool. Nevertheless, the prevalence of malnutrition changed according to diagnostic tool used. The prevalence of malnutrition was 18.7% using the MNA (long or short form), but it was greater if other diagnostic criteria were used (BMI, albumin, or weight loss) (45.7%). The prevalence of malnutrition, of risk of malnutrition, and the diagnostic tool used in each study are presented in Table 1.

In this section we included 10 studies that assessed the nutritional status of older people with hip fracture, with a total of 1575 subjects (88.3% female, mean age 79.6 $\pm$ 4 years). The design of the studies, the general characteristics of the populations studied, and the main results are presented in Table 2.

Patients with hip fracture present malnutrition, as demonstrated by the presence of low values of the anthropometric indices. Several studies showed that energy intake in older people is smaller than that required and recommended [12–15]. They also showed that calorie and protein intake are significantly lower in geriatric patients with hip fracture compared to patients without fracture. Both the reduced intake observed in hip fracture patients and the increase of the energy requirement secondary to the inflammatory state lead to weight loss and a reduction in muscle mass and fat tissue indicators, and this hypercatabolism situation may continue up to 4 months after the fracture [16–18].

The importance of a good nutritional status was backed up by studies that observed how higher BMI scores were associated with a lower incidence of hip fractures [19]. An interesting and original study showed that patients with intracapsular fractures presented lower BMI scores than patients with intertrochanteric fractures. Almost half of the subjects with intracapsular fractures presented BMI scores lower than 18 kg/m^2, versus only one-fifth of patients with intertrochanteric fractures [20].

Table 1. Prevalence of malnutrition or risk of malnutrition and nutritional screening tool used in the included studies.

Reference	Total *n*	WN *n*	RMN *n*	MN *n*	Cut-Off for Malnutrition
[21]	17,651	9549	-	8102	Albumin < 3.5 g/dL
[22]	173	49	-	57	BMI < 22 kg/m^2
[23]	23	9	7	7	BMI †
[20]	96	59	-	37	BMI < 18.5 kg/m^2
[24]	60	34	-	26	Weight loss ≥ 5% 1 m, or ≥ 10% 6 m, and/or albumin < 2.7 g/dL
[14]	25	11	11	3	Hospital's own screening tool §
Total of subjects	18,028	9711	18	8232	
Percentage		53.9%		45.7%	
Reference	**Total *n***	**WN *n***	**RMN *n***	**MN *n***	**Cut-Off for Malnutrition**
[15]	49	18	23	8	MNA ‡
[19]	80	38	35	7	MNA
[25]	127	89	36	2	MNA
[17]	50	32	18	0	MNA
[26]	50	7	29	14	MNA
[27]	97	44	37	16	MNA
[28]	162	59	-	103	MNA
[29]	152	87	-	65	MNA
[18]	215	95	95	25	MNA-SF ¥
[30]	204	55	98	51	MNA-SF
[31]	594	316	236	42	MNA-SF
[32]	415	152	185	78	MNA-SF
Total of subjects	2195	992	774	411	
Percentage		45.2%	35.3%	18.7%	

§ This screening tool is based on changes in dietary intake, weight, and other risk factors (pressure ulcers, presence of infection, period of fasting, and the need for help with eating and drinking); † Risk of malnutrition cut-off point: Body Mass Index (BMI) between 20 and 22 kg/m^2; ‡ Mini-Nutritional Assessment (MNA) cut-off points: well-nourished ≥ 24 points, at risk for malnutrition at 17–23.5 points, and malnourished at less than 17 points; ¥ Mini-Nutritional Assessment-Short Form (MNA-SF) cut-off points: well-nourished 12–14 points, at risk of malnutrition 8–11 points, and malnourished 0–7 points; WN: well-nourished; RMN: risk of malnutrition; MN: malnourished.

Table 2. Nutritional status and biomarkers in patients with hip fracture.

Authors **Origin** **Publication Year**	**Design** **Aim** **Setting**	***n* (Male/Female)** **Age, Mean ± SD (Years)** **BMI (kg/m^2)**	**Anthropometry** **Measurement of Body Composition** **Biomarkers**	**(1) Exclusion Criteria** **(2) Definition of Malnutrition**	**Main Outcomes**
Mansell UK 1990 [33]	Observational Comparison of anthropometric measurements of women with HF, with healthy volunteers in the community (C) and patients admitted to geriatric wards (G)	*n* 663 (0/663) HF 470 Community 103 Geriatric 90 HF = 77.3 ± 0.3 years Community 72.5 ± 0.5 years Geriatric 79.1 ± 0.8 years	MAC (cm) HF 22.8 ± 0.2 Community 28.6 ± 0.27 Geriatric 25.9 ± 0.41 TSF (mm) HF 13.0 ± 0.6 Community 24.7 ± 0.6	(1) For healthy female: housebound or wheelchairs (2) NA	Fractured group were older than healthy subjects ($p < 0.001$). HF vs. Community: ↓ MAC ↓ AMA ↓↓ TSF ↓↓ AFA ($p < 0.001$) Significant MAC reduction per year of age: −0.20 ± 0.03 cm/year (HF) −0.15 ± 0.06 cm/year (Community) Significant TSF reduction per year of age: −0.16 ± 0.03 mm/year (HF)
Maffulli UK 1999 [20]	Observational Nutritional differences in patients with intertrochanteric (IT) and intracapsular (IC) fractures	*n* 119 (91/28) IT 17–54 IC 11–37 80.8 ± 9.1 years 21.5 ± 4.1 kg/m^2	**Intertrochanteric** TSF 11.6 ± 4.5 mm BSF 6.1 ± 4 mm MAC 23.5 ± 3.6 cm **Intracapsular** TSF 10.6 ± 4 mm BSF 5.4 ± 2.4 mm MAC 21.9 ± 3.1cm	(1) Pathologic fracture (2) BMI < 18 kg/m^2	Malnourished → 45% IC vs. 20% IT ($p < 0.001$) 19% Overweight or obese → 22% IT vs. 2% IC Complications 15% IC vs. 3% IT ($p < 0.05$) BMI: IC < IT (20.1 ± 3.3 vs. 22.5 ± 4.6 kg/m^2, $p < 0.01$)
Murphy UK 2000 [15]	Observational Assess the sensitivity and specificity of MNA, and its comparability with other nutritional tools	*n* 49 (0/49) 79.5 ± 9 years 23.7 ± 4.3 kg/m^2	Albumin 36.9 ± 4.7 g/L	(1) Cognitive impairment (2) MNA	Patients had low mean values for body weight, albumin and transferrin Mean energy intake was below the estimated average requirementMNA < 17: Sensitivity: 27–57% Specificity: 66–100%
Lumbers UK 2001 [12]	Cross-sectional Intake and nutritional status in HF compared to day center attendees (DC)	*n* 125 HF 75 (0/75) DC 50 (0/50) 80.2 ± 7.9 years 25.5 ± 4.8 kg/m^2	**HF** MAC 27.1 ± 4.3 cm TSF 17 ± 2.7 mm MUAMC 21.4 ± 3.4 cm **Day Centers** MAC 31.3 ± 4.7 cm TSF 18.9 ± 2.8 mm MUAMC 23.3 ± 3.8 cm	(1) Mental function test < 7 (2) NA	HF patients vs. day center attendees have: lower BMI (24.1 ± 4.7 vs. 27.5 ± 4.9 kg/m^2, $p < 0.001$); lower MUAMC, albumin, proteins and energy intake and higher CRP ($p < 0.01$) Albumin ↔ RCP ($r = -0.45$)
Nematy UK 2006 [14]	Observational Nutritional status and energy intake	*n* 25 (7/18) 85.3 ± 1.5 years 21.9 ± 1.0 kg/m^2	Albumin 36 ± 2.6 g/L	(1) Pathological fracture or elective surgery (2) Changes in dietary intake, weight loss, pressure sore, infection, and need help for eating	At risk of malnutrition group (*n* 17) had lower BMI and lower energy intake versus well-nourished group (*n* 8) BMI: ARM 19.6 ± 1.1 vs. WN 25 ± 1.5 kg/m^2 Energy intake: ARM 3602 ± 320 vs. WN 5044 ± 528 kJ/day

Table 2. *Cont.*

Authors Origin Publication Year	Design Aim Setting	*n* (Male/Female) Age, Mean ± SD (Years) BMI (kg/m^2)	Anthropometry Measurement of Body Composition Biomarkers	(1) Exclusion Criteria (2) Definition of Malnutrition	Main Outcomes
Perez Spain 2010 [19]	Observational Prevalence of malnutrition	*n* 80 (24/56) 80.6 ± 6.3 years 27.1 ± 4.4 kg/m^2	TSF 5.5 ± 2.3 mm BSF 8.1 ± 4.8 mm MAC 26.8 ± 3.9 mm CC 31.9 ± 4 cm	(1) NA (2) MNA	Length of hospital stay: men 15.3 ± 5.8 days; women 14.9 ± 12 days MNA ↔ BMI r = 0.6
Perez Spain 2011 [13]	Observational Nutritional status and intake of HF vs. community dwelling study participants	*n* 86 (0/86) HF = 44 Community = 42 **Age** HF = 77.9 ± 4.7 years Community = 76.2 ± 4.6 years **BMI kg/m^2** HF = 27.6 ± 3.7 Community = 31.3 ± 4.6	**MAC (cm)** HF 27.3 ± 3.2 Community 29.1 ± 4.1 **Calf circumference (cm)** HF 32.5 ± 3.6 Community 35.1 ± 4.4	(1) No osteoporotic fractures or major trauma (2) NA	HF has lower BMI, arm and leg circumference than community dwelling (p < 0.05) Energy intake (kcal): HF 1417; community dwelling 2052 (p < 0.001) Calcium (mg/dL): HF 827; community dwelling 1265 (p < 0.001) Vitamin D (µg/dL): HF 1.6; community dwelling: 5.2 (p < 0.001)
Koren-Hakim Israel 2012 [18]	Retrospective Association of MNA-SF with functional status, comorbidity, and mortality (36 months)	*n* 215 (61/154) 83.5 ± 6.1 years 26.4 ± 4.9 kg/m^2	WN28.1 ± 4.0 kg/m^2 ARM 25.5 ± 5.1 kg/m^2 MN 22.7 ± 3.7 kg/m^2	(1) Terminal illnesses and multi-trauma (2) MNA	MNA ↔ BMI, ADL, cognitive status, readmission, mortality 36 m, CCI and CIRS-G Independent variables for mortality → Charlson comorbidity index and functional status (ADL)
Villani Germany 2013 [34]	Cross-sectional Evaluate new screening tool for detection cachexia	*n* 71(19/52) 82.2 ± 5.8 years Men 23.9 ± 2.9 kg/m^2 Women 25.9 ± 3.8 kg/m^2	M: MAC (cm) 26.7 ± 3.3 TSF (mm) 11.5 ± 4.8 W: MAC (cm) 27.1 ± 3.9 TSF (mm) 16.4 ± 5.4	(1) Pathological fracture or malignancy, residing in residential care (2) NA	Patients with cachexia: 5 new tool 4 (consensus definition) New tool: Sensitivity 75% and specificity 97% Positive predictive value 60%, negative predictive value 99%
Bell Australia 2014 [35]	Prospective Concurrent and predictive validity of malnutrition diagnostic measures	*n* 142 (45/97) 83.5 years	NA	(1) NA (2) MNA-SF < 8 BMI < 18.5 kg/m^2 ALB < 35 g/L ICD10-AM Geriatrician (subjective clinical assessment)	Malnutrition prevalence with different tools: BMI (12.7%), MNA-SF (27%), ICD10-AM (48.2%), Albumin (53.2%), subjective assessment (55.1%) MNA-SF ↔ ICD10-AM (r = 0.3) and BMI (r = 0.2) ICD10-AM ↔ subjective assessment (r = 0.6) ICD10-AM independent predictor of 4-month mortality (OR 3.6, 95%CI 1.1–11.8)

ADL: activities of daily living; AFA: arm fat area; AMA: arm muscle area; ARM: at risk of malnutrition; BMI: body mass index; BSF: biceps skinfold; CIRS-G: cumulative illness rating scale for geriatrics; CRP: C-reactive protein; HF: hip fracture; ICD10-AM: international classification of disease 10th revision-Australian modification; MAC: mid-arm circumference; MN: malnourished; MNA: Mini Nutritional Assessment; MUAMC: mid-upper arm muscle circumference; TSF: triceps skinfold; WN: well-nourished. . ↓: lower; ↓↓ much lower; ↔: correlation.

3.2. Influence upon Outcomes and Complications

The general characteristics of the studies included in this section can be found in Table 3.

Espaulella et al. showed how after 6 months' follow-up only slightly over half of the patients subject to follow-up had recovered the functional status they had before the fracture [36]. The MNA was an independent predictor of functional status upon discharge [30], at four and at 12 months [31]. Malnourished patients are more likely to suffer postoperative delirium [32], as well as other post-operative complications such as sepsis [21] and pressure ulcers [37].

Malnutrition is of double importance as it is a risk factor for hip fracture, and in patients with hip fracture it reduces the ability to recover pre-fracture functional capacity. Indeed, malnutrition is a risk factor for fracture, and malnourished older people generally present a worse functional status before the fracture and frequently recover only partially their pre-fracture level of independency in activities of daily living (ADL) following a hip fracture [27]. Conversely, well-nourished older people tend to improve their functional status at discharge after a hip fracture, as revealed by the motor-Functional Independence Measure (FIM) scale [30].

Malnutrition and risk of malnutrition are more prevalent in geriatric patients with a higher comorbidity [38], in addition to being risk factors for complications following hip fracture surgery, such as pressure ulcers [39].

Albumin could be a good blood marker of malnutrition [40]. In this context, Bohl et al. studied a large database (17,651 patients with hip fracture, mean age 84.4 $\pm$ 7.2 years) and observed a prevalence of malnutrition of 45.9%, defined as albumin values below 3.5 g/dL prior to surgery [21]. These authors reported that patients with hypoalbuminemia presented a higher prevalence of sepsis ($p < 0.001$), longer hospital stay ($p < 0.001$), and higher prevalence of readmission ($p = 0.054$). The benefits of a good nutritional status were also observed in other studies [18].

Table 3. Association of nutritional status, as revealed by nutritional biomarkers, with outcomes and post-operative complications.

Authors Origin	Design Aim	*n* (Male/Female) Age, Mean ± SD (Years)	BMI (kg/m^2) Biomarkers	Exclusion Criteria MN Definition Tool	Main Outcomes
Formiga Spain 2005 [41]	Prospective observational Relationship between nutritional status and complications	*n* 73 (12/61) 81.5 ± 7.1 years	Cholesterol 4.3 ± 1.1 mmol/L Albumin 30.6 ± 3.6 g/L TLC/mm^3 1278 ± 463	Pathological or multiple fractures, terminally ill patients, surgery delayed >48 h or lipid-lowering drug MNA-SF <11	MNA-SF → 11 ± 0.5 MNA-SF not predict → nosocomial infections and pressure ulcers Albumin predict → nosocomial infections ↓ TLC years ↓ Albumin predict → pressure ulcers Barthel index ↔ Charlson comorbidity index $r = -0.9$ ($p < 0.0001$) Length of hospital stay = 16.4 days
Montero Spain 2007 [42]	Prospective cohort Relationship between malnutrition and recovery	*n* 110 (22/88) 81.4 ± 7.3 years	25(OH)vitD 10.8 ± 5.3 ng/ml TLC/ mm^3 1545 ± 592 Albumin 32.6 ± 3.8 g/L Prealbumin 15.3 ± 4.7 mg/dL Cholesterol 160.5 ± 40.8 mg/dL Transferrin 195.9 ± 47.1 mg/dL	Pathologic or major trauma fractures Anthropometric and blood biomarkers	38.8% regained pre-fracture functional state Dementia ↔ ↓ functional recovery 25(OH)vit D <10 ng/ml ↔ ↓ pre-fracture functional state, with bedridden (1 year) and with no functional recovery ($p < 0.05$) Factors associated to bedridden (1 year) OR, 95%CI - pre-fracture functional status 10.02, 2.83–35.47 $p < 0.01$ - Caloric malnutrition 9.57 (2.18–42.84) $p < 0.01$ - Protein malnutrition 15.23 (1.36–1.70) $p < 0.05$
Baumgarten USA 2009 [37]	Prospective cohort Identify care settings associated with increased pressure ulcers risk	*n* 658 (152/506) 83.2 ± 6.6 years	23.8 ± 5.1 kg/m^2	Fractures occurred during hospital stay Subjective Global Assessment (SGA)	Pressure ulcers at baseline ↔ ↑ severe illness, ↑ comorbidity, ↓ nutritional status, ↓cognitive status ($p < 0.05$) Albumin < 30 g/L: 31.5% Length of hospital stay 5.6 ± 2.8 (no pressure ulcers) vs. 6.6 ± 3.8 (pressure ulcers) ($p < 0.001$)
Drevet France 2014 [26]	Prospective observational Protein Energy Malnutrition prevalence	*n* 50 (15/35) 86.1 ± 4.4 years	22.6 ± 4.3 kg/m^2	Road accident MNA	Prevalence of PEM was 28% (*n* 14) Mean hospital stay: PEM 21.9 ± 16.7 vs. 13.4 ± 6.7 in non-PEM ($p = 0.012$)
Goisser Germany 2015 [27]	Observational Relationship between nutritional status (MNA) and functional and clinical course	*n* 97 (20/77) 84 ± 5 years	NA	Terminal state, cancer-related pathologic fractures, cancer with acute radiation or chemotherapy MNA	Patients at risk for malnutrition and malnourished: - Baseline, ↑ comorbidities ↑ Charlson comorbidity index ↑ pressure ulcers ↓ cognitive status ($p < 0.05$) - All times, ↓ ADL score ($p < 0.05$) - 68% did not regain pre-fracture ADL - 18% did not regain pre-fracture mobility level ($p = 0.02$)

Table 3. *Cont.*

Authors Origin	Design Aim	*n* (Male/Female) Age, Mean ± SD (Years)	BMI (kg/m^2) Biomarkers	Exclusion Criteria MN Definition Tool	Main Outcomes
Bohl USA 2017 [21]	Retrospective Association between albumin with death, and postoperative complications	*n* 17,651 (12,595/5056) 84.4 ± 7.2 years	24.6 ± 5.6 kg/m^2 Albumin 35 ± 5 g/dL	Preoperative serum albumin concentration not available Albumin concentration	18.5% had BMI < 20 kg/m^2 Patients with hypoalbuminemia had higher rates: - of death (RR 1.52. 95%CI 1.37–1.70. $p < 0.001$) - of sepsis (RR 1.92. 95%CI 1.36–2.72. $p < 0.001$) - of longer legnth of hospital stay, 5.7 ± 4.7 vs. 5.0 ± 3.9 days ($p < 0.001$)
Helminen Finland 2017 [31]	Prospective Prognostic significance of MNA and albumin	*n* 594 (169/425) 84 years	24.9 kg/m^2 Albumin 33.5 g/L	Pathological or periprosthetic fractures, institutionalization, prefecture inability to walk MNA-SF	All nutritional measures were significantly associated with mortality Being at risk for malnutrition or being malnourished were significantly associated with impaired mobility at 4 months and 1 year
Mazzola Italy 2017 [32]	Prospective If nutritional status predict postoperative delirium	*n* 415 (104/309) 84 ± 6.6 years	NA Albumin 33 ± 5.4 g/L	Nonoperative approach and preoperative delirium MNA-SF	Risk to develop postoperative delirium: - at risk for malnutrition: OR 2.42, 95%CI 1.29–4.53 - malnourished: OR 2.98, 95%CI 1.43–6.19
Inoue Japan 2017 [30]	Prospective Relationship between nutritional status and functional recovery	204 (39/165) 82.7 ± 9.2 years	20.2 ± 2.5 kg/m^2 Albumin 36 ± 9 g/L	Terminal disease, chronic liver disease, pre-fracture ambulation difficulty, no weight-bearing, discontinued postoperative rehabilitation MNA-SF	Well-nourished had higher motor-FIM score at discharge Motor-FIM at discharge was significant associated with MNA-SF

ADL: activities of daily living; BMI: body mass index; FIM: functional Independence Measure; HF: hip fracture; MNA: Mini Nutritional Assessment; PEM: protein energy malnutrition; OR: odd-ratio; 95%CI: 95% confidence interval. ↔: correlation.

3.3. Malnutrition and Mortality in Older People with Hip Fractures

In this section we included those studies whose main objective was to assess the impact of malnutrition, as revealed by nutritional biomarkers, on mortality. In addition, we considered studies where a multivariable analysis was carried out and which included malnutrition biomarkers. A summary of the design, characteristics, and main results of the included studies can be found in Table 4. We included five studies, with a total of 2518 patients (71.8% females), mean age 84.3 ± 7.2 years.

Mortality was inversely associated with pre-surgery albumin levels, and patients with hypoalbuminemia had a relative risk of dying of 1.52 (95% Confidence Interval (CI) 1.37–1.70, $p < 0.001$) [21]. Regardless of the tool used to diagnose malnutrition, low values of albumin or BMI or low MNA were associated with an increase in mortality. Albumin concentrations of less than 36 g/L were associated with a 4-year mortality nearly six times greater (Odd-Ratio (OR) 5.85, 95% CI 2.3–16.5) [43]. Furthermore, BMI values of less than 22 kg/m^2 were associated with an increase of almost seven times the mortality at 1 year, as compared to values higher than 25 kg/m^2 (Hazard Ratio (HR) 7.25, 95% CI 1.6–33.7) [22]. Studies such as that of Flodin and collaborators confirm the anterior outcome, observing that subjects with a BMI greater than 26 kg/m^2 had a risk almost three times less of dying after 1 year from the fracture (OR 2.6, 95%CI 1.4–5.0) [44].

Cenzer et al. showed that difficulty preparing meals after hip fracture predicts 1-year mortality (and this predictor factor has the same points as congestive heart failure) [45]. Others factors such as age, male sex, congestive heart failure, and not being able to drive complete the risk stratification scale [45].

Mortality increases progressively after a hip fracture, from an in-hospital mortality of 7%, to 11% in the first 6 months after the fracture, up to 30% in the first year and 40% at 3 years. To highlight the importance of this health problem, we summarized total mortality and the follow-up periods of the included studies in Table 5.

Table 4. Relationship between nutritional status and mortality.

Authors **Origin** **Year** **Design**	***n* (Male/Female)** **Age, Mean ± SD (Years)**	**BMI kg/m^2** **(Mean ± SD)**	**Exclusion Criteria**	**Main Outcomes**
Miyanishi Japan 2010 Retrospective [43]	*n* 129 (24/103) 79 years Survivors 78 ± 11 years Non-survivors 81 ± 10 years	21 ± 2.9 (Survivors) 18.9 ± 3.5 (Non Survivors)	NA	Non-survivors have: ↓* BMI, hemoglobin, albumin and ↑* dementia, complications Mortality predictors (4-year mortality): Albumin (<36 g/L) OR = 5.85 and BMI (<18.9 kg/m^2); OR = 1.16
Schaller Switzerland 2012 Sub-analysis of RCT [22]	*n* 173 (36/137) 84.2 ± 6.7 years	NA	Severe cognitive impairment (MMSE > 15) or delirium	Risk factor for ↑mortality (1-year mortality): MMSE <25 (HR = 5.77, 95%CI: 1.55–21.55) Male sex (HR = 3.55, 95%CI: 1.26–97) BMI <22 vs. >25 (HR = 7.25, 95%CI: 1.61–33.74) Vitamin D per 1ng/ml (HR = 0.93, 95%CI: 0.87–0.998)
Gumieiro Brasil 2013 Prospective [46]	*n* 86 (20/66) 80.2 ± 7.3 years	NA	Pathological fracture	MNA ↔ gait impairment OR = 0.77 (0.66–0.90) p = 0.001 ↑ 1 point MNA → ↑* 29% chance of walking MNA ↔ mortality HR = 0.87 (0.76–0.99) p = 0.04 ↑ 1 point MNA → ↓* 15% mortality risk
Flodin Sweden 2016 Prospective [44]	*n* 843 (227/616) 82 ± 7 years	22.7 ± 3.8 kg/m^2	Severe cognitive impairment, admitted from nursing-homes	1-year mortality (p = 0.006): BMI > 26 = 6% BMI 22–26 = 18% BMI < 22 = 16% BMI > 26 indicates a higher likelihood of returning to independent living (OR 2.6, 95%CI 1.4–5.0)
Uriz-Otano Spain 2016 Prospective [47]	*n* 430 (97/333) 84.2 ± 7.4 years	NA	Tumor, high impact fracture	3-year mortality: Albumin HR 0.61, 95%CI 0.42–0.90 Predictors of 3-year mortality: Age, HR 1.04, 95%CI 1.01–1.06 Comorbidity, HR 1.19, 95%CI 1.09–1.30 Complications, HR 1.17, 95%CI 1.05–1.31

MMSE: Mini-Mental State Examinatio; RCT: randomized clinical trial; ↓*: significantly less; ↑*: significantly more.

Table 5. Total mortality during hospital stay, and at various stages after discharge.

Reference	In-Hospital	<6 Months	1 Year	36 Months	>36 Months	*n*
[18]	6%			36.7%		215
[20]	6%					119
[21]	7.4%					17,651
[22]			27%			173
[27]	15%					97
[29]		7.70%				152
[31]		30%	26%			594
[35]	4.9%	14.8%				142
[36]	4%	21.1%				171
[39]		29.1%	42.40%			420
[41]	10%					73
[42]	6.4%	11.8%	19.4%			110
[43]					48%	129
[45]			27%			857
[46]		12.8%				86
[48]	1.7%	17.9%				57
[49]	11.6%	20.6%				302
						23,093
Total mortality (%)	7.4%	20.4%	29.3%	39.4%	48%	

3.4. Effects of Nutritional Intervention

In this section we included the studies in which nutritional interventions were carried out. The general characteristics of the populations included, the design, and the main results of the studies included are presented in Table 6.

We included 18 studies, 14 of which were carried out in Europe, one in the USA, one in Australia, and two in Asia, totaling 2248 patients (each study including between 23 and 420 subjects), with an mean age of 81.6 $\pm$ 5.4. Five studies were carried out only on women, whereas the rest had mixed samples (66.8% women).

A majority of the studies (*n* 14) used oral nutritional supplements. One was preceded by supplementation with parenteral nutrition. In one study the supplement was administered via naso-gastric tube, and in one other study only dietary advice was used. One study did not specify the type of intervention. The characteristics of the interventions, calories used, protein content, and duration of the treatment are summarized in Table 7.

Regarding duration, in seven studies intervention was maintained during hospital stay, in four studies the duration was $\leq$3 months, and in two it was up to 6 months. Two of the studies did not specify the duration of treatment.

The results demonstrated that a good compliance in the use of oral supplements was associated with an increase in total energy, protein, and liquid intake during hospital stay [16,17,23,24,48]. This is important because higher nutritional intake was associated with less postoperative complications. This improvement in intake brought on an increase of IGF-1, a decrease of bone loss 1 year after the fracture [50], lesser prevalence and intensity of delirium, and lower production of oxidative stress-derived products [23]. Nutritional supplementation could also lead to a decrease in the incidence and duration of pressure ulcers, as well as delay their onset. Weight loss was found among subjects who received no supplementation (the control group) [25,51,52], probably due to a loss of muscle mass mboxciteB53-nutrients-273625,B54-nutrients-273625. Two recent studies used supplements enriched with Calcium β-Hydroxy-β-Methylbutyrate (CaHMB); these studies observed an improvement in muscle indices in the intervention groups but no improvement in the control groups [54,55].

A multidisciplinary approach is required in order to reduce malnourishment in subjects admitted to hospital [25]. Having a dietician on the team [49] as well as nurses trained in nutrition [25] was associated with an increase in energy, protein, and supplement intake. In addition, a multidisciplinary approach was shown to counteract increases in the incidence of malnutrition after discharge [25]. Furthermore, nutritional intervention was associated with lower short- and long-term mortality rate as well as with an increase in quality of life (as revealed by the EuroQol-5D scale) [25,49]. Nutritional advice for well-nourished patients was associated with better performance in the ADL, and with a better recovery of the ability to walk [28].

Table 6. Nutritional intervention in patients with hip fracture.

Author **Year** **Origin**	**Design** **Aim**	***n* (Male/Female)** **Age, Mean ± SD (Years)** **Follow-Up (FU)**	**BMI kg/m^2 (Mean ± SD)** **Measurement of Body Composition**	**Exclusion Criteria**	**Results**
Schürch [50] 1998 Switzerland	RCT Effects of oral protein supplements on bone metabolism	*n* 82 (8/74) IG 41 CG 41 80.7 ± 7.4 years 6 months	24.3 ± 4.0 kg/m^2 MAC (cm) 24.1 ± 3.1	Pathologic fracture, fracture caused by severe trauma, history of contralateral hip fracture, severe mental impairment, bone disease, renal failure, and life expectancy < 1 year	IG (at 6m): ↓ rehabilitation stay (42.2 ± 6.6 vs. 53 ± 4.6 days) $p = 0.018$ ↑increase IGF-1 and IgM $p < 0.05$ 50% reduction of proximal femur bone loss (1 year)
Espaulella [36] 2000 Spain	RCT Nutritional supplement and functional recovery, complications and mortality	*n* 171 (36/135) IG 85 CG 86 82.6 ± 6.6 years Follow-up: 6 months	25.4 ± 5 kg/m^2 MAC: 24.6 ± 3.8 cm Albumin: 35 ± 5.5 g/L	Advanced dementia, intravenous nutrition, pathologic fractures, and accidental falls	Patients with ≥1 complication (6 months): IG 44 (55%) CG 57 (70.4%) $p = 0.04$ IG: ↑ increase albumin (3 months and 6 months)
Bruce [51] 2003 Australia	RCT Nutritional supplements and prevention of weight loss and improvement of outcomes	*n* 109 (0/109) IG 50 CG 59 83.9 ± 7.7 years Follow-up: 6 months	22.8 ± 2.6 kg/m^2 Albumin 38.8 ± 4.1 g/L	BMI < 20 or BMI > 30 kg/m^2, residents of nursing homes, diseases that influence nutritional intake, diabetes, and fracture due to a major trauma	Weight loss (all patients): At 4 weeks 31.5% > 5% weight loss 20.7% > 7.5% weight loss At 8 weeks 27.4% > 5% weight loss 14.6% > 5% weight loss Fewer weight loss ↔ ↑ number of cane ($p = 0.019$) and ↑duration of supplementation ($p < 0.05$)
Houwing [56] 2003 The Netherlands	RCT Effect of a high-protein supplement on the development of pressure ulcers	*n* 103 (19/84) 81.0 ± 1.1 years	23.9 ± 0.5 kg/m^2	Terminal care, metastatic hip fracture, insulin-dependent diabetes, renal disease, hepatic disease, BMI > 40 kg/m^2.	55.3% developed pressure ulcers stage I or II. Incidence of pressure ulcers stage II: supplement 18%, placebo 28% 57% of patients developed pressure ulcers by the second day
Sullivan [48] 2004 USA	RCT Efficacy of enteral nutrition to decrease complications and long-term outcomes	*n* 57 (39/19) IG 27 CG 30 79 ± 7.6 years Follow-up: 6 months	22.1 ± 4.4 kg/m^2 BSF: 6.4 ± 3.3 mm Albumin: 33.9 ± 4.5 g/L	Pathological fracture, significant trauma to other organ systems, metastatic cancer, cirrhosis of the liver, and organ failure	IG: ↑ intake of total nutrients $p = 0.012$ At discharge: ↑ Albumin: IG 29 ± 5 vs. CG 25 ± 5 g/L $p = 0.002$

Table 6. *Cont.*

Author **Year** **Origin**	**Design** **Aim**	***n* (Male/Female)** **Age, Mean ± SD (Years)** **Follow-Up (FU)**	**BMI kg/m^2 (Mean ± SD)** **Measurement of Body Composition**	**Exclusion Criteria**	**Results**
Tidermark [53] 2004 Sweden	RCT Effects of nutritional treatment on nutritional and functional status	*n* 60 (0/60) 82.9 ± 5.4 years Follow-up: 12 months	20.4 ± 2.3 kg/m^2	<70 years, BMI > 24 kg/m^2, cognitive impairment and institutionalized, dependent to walk, fractures older than 24 h, pathological fractures, rheumatoid arthritis.	Lean body mass decreased in the CG and protein groups, but remained the same in the protein plus nandrolone group. ADL declined only in the CG.
Eneroth [16] 2005 Sweden	RCT Effects of nutritional supplements on nutritional status and intake.	*n* 80 IG 40 (7/33) CG 40 (10/30) 81.4 ± 7.6 years	23.9 ± 3.8 kg/m^2	Multiple and pathologic fractures, malignant disease, inflammatory joint disease, dementia, depression, acute psychosis, epileptic seizures, insulin-treated diabetes mellitus, heart, kidney, or liver insufficiency	PEM baseline: CG 33%, IG 38% Fluid intake: IG = 1856 ml, CG = 1300ml ($p < 0.0001$) Energy intake during days 1–10: IG = 1296 kcal/day CG = 916 kcal/day ($p = 0.003$) Difference between actual and needed energy intake: IG = −228 kcal/day CG = −783 kcal/day ($p = 0.0003$)
Duncan [49] 2006 UK	RCT Effectiveness of dietetic assistants (DAs) to reduce in-hospital and 4 months mortality.	*n* 302 (0/302) GT 145 GC 157 83.5 years Follow-up: 4 months	NA	Pathologic fracture	Mortality In trauma unit IG 4%, CG 10% ($p = 0.048$) At 4 months IG 13%, CG 23% ($p = 0.036$) - Energy intake = IG 1105; CG 756 kcal/day ($p < 0.001$) - Supplement intake: IG 409; CG123 kcal/day ($p < 0.001$) - MAC change: IG −0.9; CG −1.3 cm ($p = 0.002$) Weight change: IG −0.35; CG −1 kg ($p = 0.16$)
Hommel [39] 2007 Sweden	Quasi-experimental Effects of an improved care intervention in relation to nutritional status and pressure ulcers	*n* 420 IG 210 (70/140) CG 210 (62/148) 81 ± 10.4 years	24.3 ± 4.4 kg/m^2 MAC 27.7 ± 4.4 cm TSF 14.8 ± 6.8 mm	NA	Length of hospital stay: IG 11.8 ± 7.4 vs. CG 10.8 ± 5.8 days Pressure ulcers: IG 10%; CG 20.5% ($p = 0.009$)
Botella-Carretero [24] 2010 Spain	RCT Effect of perioperative supplements on nutritional status and postop complications	*n* 60 (16/44) IG 30 (6/24) CG 30 (10/20) 83.6 ± 5.8 years	24.4 ± 3.1 kg/m^2 TSF 11.9 ± 4.1 mm MAC 24.4 ± 3.2 cm MNA 18.6 ± 3.4 Albumin 33 ± 4g/L	Weight loss > 5% in 1 month or weight loss > 10% in 6 months, albumin < 27 g/L, renal failure, hepatic insufficiency, respiratory failure, and any gastrointestinal condition, any nutritional support in the past 6 months	CG: decrease and worse recovery of albumin and prealbumin ($p = 0.002$; $p = 0.001$) IG: ↑ energy and protein intake ($p = 0.042$; $p < 0.001$) ↑ protein intake → ↓ post-operative complications OR = 0.925 (0.869–0.985) ($p = 0.003$)

Table 6. *Cont.*

Author Year Origin	Design Aim	*n* (Male/Female) Age, Mean ± SD (Years) Follow-Up (FU)	BMI kg/m^2 (Mean ± SD) Measurement of Body Composition	Exclusion Criteria	Results
Fabian [23] 2011 Austria	RCT Effect of nutritional supplement on post-operative oxidative stress and length of hospital stay	*n* 23 (0/23) IG 14 CG 9 83.8 ± 7.4 years Follow-up: 3 weeks	21.2 ± 3.4 kg/m^2 Albumin 36.6 ± 3.8 g/L	Renal disease, liver failure, severe congestive heart failure, severe pulmonary disease, and any gastrointestinal condition that might preclude the patient from adequate oral nutritional intake	IG ↑ energy and protein intake ($p < 0.05$) Albumin, total protein, and total antioxidant capacity (post-operative): ↓ CG ($p < 0.05$) ↓ IG Advance oxidation protein products and malondialdehyde: in CG levels still elevated during time but not in IG Length of hospital stay: IG 17 ± 4 vs. CG 19 ± 9 days Albumin ↔ CRP and total antioxidant capacity ($p < 0.05$) Length of hospital stay ↔ AOPP and MDA ($p < 0.01$)
Hoekstra [25] 2011 The Netherlands	Prospective Effectiveness of a multidisciplinary intervention on nutritional status	*n* 127 (31/96) IG 61 CG 66 80.3 ± 8.3 years	26.8 ± 4.5 kg/m^2	Severe dementia, cancer, pathologic fracture, renal and hepatic dysfunction, pacemaker	IG ↑ energy intake protein, vitamin D, zinc, calcium ($p < 0.01$) IG lower reduction of EuroQol-5D ($p < 0.05$) ↓* BMI, BCM, and FM (3 months) (both groups)
Li [28] 2013 Taiwan	Randomized (1 year) Effects of protein-energy malnutrition on the functional recovery	*n* 162 (51/111) IG 80 CG 82 78.2 years	NA	Cognitive impairment, terminally ill	Malnutrition prevalence: IG 60% vs. CG 67% MN → ↓ performance of ADL, IADL, and recovery of walking ability ($p < 0.05$) IG → ↑ performance of ADL, IADL, and recovery of walking ability ($p < 0.01$)
Wyers [29] 2013 The Netherlands	RCT Cost-effectiveness of dietary intervention comprising combined dietetic counseling and ONS	*n* 152 (108/44) IG 73 CG 79 78.5 years	NA	Pathological or periprosthetic fracture, disease of bone metabolism, life expectancy < 1 year, ONS before hospital admission, dementia.	The additional cost of the nutritional intervention was only 3% of the total cost Total cost was not significantly different between both groups Nutritional intervention was likely to be cost effective for weight as the outcome over 3 months
Myint [52] 2013 Hong Kong	RCT Clinical, nutritional and rehabilitation effects of an oral nutritional supplementation	*n* 121 (41/80) IG 61 CG 60 81.3 ± 6.5 years Follow-up: 6 months	20.7 ± 2.9 kg/m^2 TSF 12.6 ± 5.6 mm MAC 24.3 ± 3 cm Albumin 29.3 ± 4.6 g/L	Tube feeding, unstable medical condition, BMI ≥ 25 kg/m^2, malignancy, contraindication for high-protein diet, and mentally incapacitated	BMI decrease of 0.25 and 0.003 kg/m^2 in the ONS group, and 0.72 and 0.49 kg/m^2 at hospital and follow-up ($p = 0.012$) Length of hospital stay was shortened by 3.8 days in the ONS group ($p = 0.04$) Intake adequate: 67% in the ONS group, 9% in the control group ($p < 0.001$)

Table 6. *Cont.*

Author Year Origin	Design Aim	*n* (Male/Female) Age, Mean ± SD (Years) Follow-Up (FU)	BMI kg/m^2 (Mean ± SD) Measurement of Body Composition	Exclusion Criteria	Results
Anbar [17] 2014 Israel	RCT Optimization of supplementation by measurement of resting energy requirements and the effect on outcomes	*n* 50 (17/33) IG 22 CG 28 83.1 ± 6.3 years	24.9 ± 3.9 kg/m^2	Presented to hospital >48 h after the injury, steroids and/or immunosuppression therapy, oncologic disease, multiple fractures, dementia	ONS = 19.6% of total energy IG: ↑ Energy and protein intake (p = 0.001) ↓ complications (p = 0.012) and infections (p = 0.008) ↓ length of hospital stay (p = 0.061) In all patients: Energy balance ↔ complications (r = −0.417; p = 0.003) and with length of hospital stay (r = −0.282; p = 0.049)
Ekinci [55] 2016 Turkey	RCT Effects of CaHMB on wound healing, mobilization, fat-free mass and muscle strength	*n* 62 (0/62) IG 32 CG 30 82.6 ± 7.1 years	22.0 ± 2.4 kg/m^2	Diabetes, renal and hepatic failure, gastrointestinal intolerance, endocrine pathology, and dementia.	Patients who were mobile on day 30: - IG 81.3% vs. CG 26.7% (p = 0.001) Muscle strength on day 30 was higher in IG vs. CG (p = 0.026)
Malafarina [54] 2017 Spain	RCT Effects of ONS on muscle mass and nutritional biomarkers	*n* 107 IG 55 CG 52 85.4 ± 6.3 years	25.4 ± 4.9 kg/m^2 Albumin 3.1 ± 0.4 g/dL	Diabetes, Barthel index <40 prior to the fracture, tumor, pathological or high-impact fractures	BMI and ALM was stable in IG, but decreased in CG. ONS (p = 0.006), function ambulation categories prior to the fracture (p = 0.007) and Barthel index prior to the fracture (p = 0.007) are protective for loss of ALM

ALM = appendicular lean mass; AOPP: advanced oxidation protein products; BCM: Body Cellular Mass; BMI = body mass index; BSF = biceps skinfold thickness; CG = control group; FM: fatt mass; IADL: instrumental activities o daily living; IGF-1 = insulin-like growth factor; HS = handgrip strength; IG = intervention group; MAC = mid-arm circumference; MNA = Mini Nutritional Assessment; ONS = oral nutritional supplement; RCT = randomized controlled trial; TSF = triceps skin fold thickness; ↓* = significantly less; ↑* = significantly more; ↔ = significant association.

Table 7. Characteristics of the nutritional intervention and composition of the nutritional supplementation used in the included studies.

Author Year Origin	Type of Supplement Administration Method	kcal	Nutritional Composition	Treatment Duration Adherence Rate (%)	Control Group
Schürch [50] 1998 Switzerland	Oral liquid supplement; single oral dose of vit D_3 200.000 UI Ca: 550 mg/day	250 kcal/day	20 g protein, 3.1 g lipid, 35.7 g carbohydrates, 90% milk proteins	5 days a week for 6 months AR: IG 73% CG 80%	Placebo: 54.5 g carbohydrates Single oral dose of vitamin D 200.000 UI Calcium: 550 mg/day
Espaulella [36] 2000 Spain	Oral liquid supplement 200 mL	149 kcal	20 g protein, 800 mg calcium, 25 IU vitamin D3	60 days AR: IG 94.1% CG 94.2%	Placebo 200 mL, 155 kcal; mainly carbohydrates
Bruce [51] 2003 Australia	Oral liquid supplement (235 mL/day)	352 kcal	17.6 g protein, 11.8 g fat, 44.2 g carbohydrate, vitamins and minerals	28 days after surgery	Hospital diet only
Houwing [56] 2003 The Netherlands	Oral liquid supplement (400 mL/day)	500 kcal	40 g protein	Immediately postoperatively during 4 weeks or until discharge AR: 75% of patients consumed >75% of daily dose	Non-caloric placebo supplement
Sullivan [48] 2004 USA	Standard care + post-operative nightly via enteral feeding tube: 1375 mL (125 mL/h) over 11 h	1031 kcal	85.8 g protein	When volitional intake exceeded 90% of estimated requirements for 3 consecutive days or was discharged: mean 15.8 ± 16.4 days AR: 83.3%	Standard care
Tidermark [53] 2004 Sweden	PR: protein-rich liquid supplement (200 mL/day) PR-N: PR + nandrolone decanoate injections (every third week) 1 g of calcium + 400 IE vitamin D3	200 kcal/day nandrolone: 25 mg intramuscular injection	20 g protein	6 months	Standard treatment 1 g of calcium + 400 IE vitamin D3
Eneroth [16] 2005 Sweden	Hospital diet + intravenous nutrition (1 l/day) followed by 400 mL/day oral supplement	Oral supplement 400 kcal/day	IV: amino acids, fat, carbohydrate, and electrolytes	3 days → IV 7 days → oral	Hospital diet only
Duncan [49] 2006 UK	NA	Mean supplement: 409 kcal/day	NA	NA	Mean standard supplement: 123 kcal/day

Table 7. *Cont.*

Author Year Origin	Type of Supplement Administration Method	kcal	Nutritional Composition	Treatment Duration Adherence Rate (%)	Control Group
Hommel [39] 2007 Sweden	Oral nutritional supplement twice a day	125 kcal/100 mL enriched with arginine, zinc, vitamins A, B, C, and E, selenium, and carotenoids	NA	From post-surgery to discharge	NA
Botella-Carretero [24] 2010 Spain	Oral nutritional supplement intake (2 × 200 mL/day)	400 kcal/day	40 g protein/day	From admission until discharge AR 52.2 ± 12.1%	Control group: no supplement
Fabian [23] 2011 Austria	Oral liquid supplement	Supplements were administered when intake of energy < 20 kcal and/or protein < 1 g/kg body weight/day	40% protein, 41% carbohydrate, 19% fat, vitamins and minerals	From post-surgery to discharge	Standard medical treatment
Hoekstra [25] 2011 The Netherlands	Nurse and doctor encouraged and motivated patients to eat and drink; if MNA < 24, dietician consulted with the patient	NA	NA	NA	Standard nutritional care
Wyers [29] 2013 The Netherlands	Oral liquid nutritional supplement (500 mL/day) Dietetic counseling	500 kcal	40 g protein	Started during hospital admission and continued until 3 months after surgery	Usual care ONS on demand: 13% received ONS and 23% received dietetic counseling
Myint [52] 2013 Hong Kong	Oral liquid nutritional supplement (240 mL twice daily) 1.2 g of calcium + 800–1000 IU vitamin D	500 kcal	18–24 g protein	Started within 3 days after admission until discharge or 28 days AR = 77.7%	NA 1.2 g of calcium + 800–1000 IU vitamin D
Anbar [17] 2014 Israel	Standard ONS (237 mL) or diabetic ONS (237 mL) Patients received the difference between intake and measured energy expenditure	355 kcal 237 kcal	13.5 g protein 9.9 g protein	Started 24 h after surgery AR = 100%	Usual hospital diet = 1800 kcal, 80 g protein

Table 7. *Cont.*

Author Year Origin	Type of Supplement Administration Method	kcal	Nutritional Composition	Treatment Duration Adherence Rate (%)	Control Group
Ekinci [55] 2016Turkey	Oral liquid nutritional supplement (220 mL twice daily)	NA	36 g protein 3 g CaHMB 1000 IU vitamin D	30 days	Usual hospital diet: 1900 kcal, 76 g protein, 63 g fat
Malafarina [54] 2017 Spain	Oral liquid nutritional supplement (220 mL twice daily)	660 kcal	60 g protein 4.6 g CaHMB 1500 IU vitamin D	During hospital admission, until discharge Mean treatment duration: 42.3 ± 20.9 days AR = all of the subjects took more than 80%	Usual hospital diet: 1500 kcal, 87 g protein, 59 g fat

4. Discussion

Malnutrition is a subject under intense discussion in geriatric research [57–59], as it is very prevalent in older people with hip fracture, it negatively influences functional recovery after fracture, it increases healthcare spending, and it is associated with high mortality. It appears that nutritional intervention aids the prevention of complications in geriatric patients with hip fracture. This review is an attempt to summarize existing evidence of these aspects. To our knowledge, this is the first review to assess the nutritional status of older people with hip fracture and how it influences complications and mortality.

Despite the variability in the main objective of the included studies, the results are homogeneous in the evidence that subjects with hip fracture have anthropometric indices indicative of malnutrition (Table 2). In addition, there is evidence that subjects with worse nutritional status have more complications (Table 3) and increased mortality (Table 4). There is a lot of variability in the main objective, as well as in the type of nutritional intervention (dietary advice, use of nutritional supplements) and in the amount of calories used in the included studies (Table 7). Despite this variability in the methods used in the studies, overall nutritional intervention has been shown to reduce complications and avoid weight loss in elderly subjects with hip fracture (Table 6).

The prevalence of malnutrition in older patients with hip fracture is higher than in community-dwelling older adults [60,61]. A further problem was associated with an increase in calorie expenditure, secondary to systemic inflammatory response, without a corresponding intake increase, whereby nutritional intake remained smaller than requirements due to factors such as pain, being bedridden, and reduced mobility [25,49].

A reduction in intake is often observed in older people, causing it to be lower than requirements [57]. These changes in intake have a multi-factor origin, among which the most frequent factors are alterations in sensory organs, loss of teeth, lack of a principal caregiver, and, in some cases, the adverse effects of certain drugs [62]. These intake alterations constitute a well-known geriatric syndrome defined as anorexia of ageing [63]. Calorie and/or protein deficits can contribute to the pathophysiology of fractures, especially through two mechanisms: (1) loss of strength and muscle mass (sarcopenia), which increases the risk of falls; and (2) low bone mineral density (osteoporosis), which reduces the resistance of bones to trauma, increasing the risk of fracture [1].

The observed variability in the parameters of nutritional status in hip fracture patients could be due to the lack of a universal consensus as to the best measure to diagnose protein-energy malnutrition. This lack of universality limits our comparison of the various studies, also making it difficult to carry out a consistent malnutrition diagnosis, which, in certain cases, can delay the clinical decision to prescribe nutritional treatment for these patients.

Despite this, the observed trend is uniform and shows that malnourished older people are at a greater risk of fracture and that the prevalence of malnutrition is high in geriatric patients admitted with hip fracture. Patients with intracapsular fracture usually have low BMI, while patients with trochanteric fracture tend to have high BMI [20,64]. Low BMI is associated with protein deficit (type II nutrients, important for maintaining weight) and type I nutrients are important for bone metabolism. In relation to this, "BMI paradox" is valid in the elderly, in which an increase in fat mass and a decrease of muscle mass are observed, and for this reason falsely high values of BMI can mask the presence of sarcopenia [65]. Despite the important limitations of the prognostic meaning of BMI in the elderly, this remains a fundamental index to assess the nutritional status for its simplicity and repeatability, and most validated nutrition assessment tools include BMI. Recent articles have proposed that the normal cut-off considered by the World Health Organization (WHO) (18.5–20.0 kg/m^2) should be modified with the values that have been shown to be associated with lower mortality in the elderly (23–29 kg/m^2) [66]. It would be advisable to complete the nutritional assessment by evaluating the body composition (with dual-energy absorptiometry (DXA) or with bioimpedance analysis) [67,68]. The problem is different if we consider the concentration of albumin for the diagnosis of malnutrition. The blood concentration of albumin may be a good nutritional index if the inflammatory state is taken

into account, considering that its concentration does not depend only on nutritional status [40]. On the other hand, albumin has been shown to be a good prognostic index in hospitalized patients [69].

Screening tools such as the Mini-Nutritional Assessment Short-Form (MNA-SF) were able to diagnose a nutritional problem before it manifested through changes in the biochemical markers of malnutrition (such as albumin or total protein) [70]. Factors such as cognitive impairment and disability in the basic activities of daily living (ADL) were associated with lower scores in the MNA-SF [71]. This tool was also shown to be a predictive factor of destination upon discharge following the fracture [72]. Selective deficiencies such as lack of vitamin D are very prevalent in older people [73].

As well as the known effects of this deficiency on bone metabolism, there is a high concentration of vitamin D receptors in muscle tissue [7]. This situation could explain why the lack of this vitamin (scant diet input, little exposure to the sun, and the ability to make vitamin D within the skin declines with age) is so obviously associated with reduced muscle strength and a worse functional status, involving factors that increase the risk of fall and fracture [42].

The high prevalence of malnutrition in people with dementia could be one of the pathophysiological mechanisms for the high risk of falls and fractures, as well as for their poor functional recovery after a fracture [27,37,42,74]. People with dementia suffered an increase in incidence of hip fracture, as dementia is a risk factor for hip fracture [75]. Strategies for the prevention of hip fractures are very important in people with dementia because they present a higher prevalence of complications, higher risk of institutionalization, and worse functional recovery [3]. Moreover, dementia is an independent predictor for mortality [76].

Malnutrition, which is very prevalent in geriatric patients with hip fracture, is associated with the incidence of complications, with length of hospital stay (and thus increase in cost), and with mortality. Hip fracture continues to be a pathology with high mortality. In spite of the achievement of a reduction in the incidence of hip fractures, mortality has not decreased [77]. Intra-hospital mortality of elderly patients with hip fracture (7.4%) is comparable with mortality of elderly patients with heart failure (8%) [78]. The problem is that hip fracture represents an acute potentially preventable disease, for example by implanting exercise programs that have been shown to reduce the risk of falling [79]. It will be necessary to improve the post-surgical treatment to reduce complications and mortality, which at 3 years is almost twice that of patients with heart failure [80,81].

Patients with hip fracture show a state of hypercatabolism secondary to reduced intake, loss of blood, and inflammation, which leads to a reduction in plasma proteins, which are important mechanisms for the defense of oxidative stress. Cell regeneration determines an increase in the production of free radicals at the site of the fracture. Plasma oxidant markers malondialdehyde (MDA) and advanced oxidation protein products (AOPP) were significantly positively, while albumin and total antioxidant capacity (TAC) are significantly negatively associated with the duration of hospitalization.

Several studies observed lower scores in nutritional indices, such as BMI, in geriatric patients who died following a hip fracture, as compared to those who lived [82]. It may be possible to reduce mortality with adequate nutritional intervention [49]. A difficult question to answer is whether nutritional supplementation is indicated for all patients with hip fracture or only for malnourished patients. Supplementation prevented weight loss in both malnourished and well-nourished patients. This association was directly related to the dose administered [51]. A higher protein intake was associated with a lower risk of post-surgery complications [24], and an adequate energy intake reduced the development of complications and was associated with a shorter duration of hospital stay [17].

Therefore, the results of this review support the indications of the European Society of Parenteral and Enteral Nutrition (ESPEN) guidelines, according to which all older adult patients with hip fracture should receive nutritional supplements during hospitalization [83].

5. Conclusions

The prevalence of malnutrition is very high in older people and increases further in older people with high comorbidities as well as in geriatric patients. Malnutrition is associated to functional alterations and this can be a cause as well as a consequence of fractures.

Malnutrition prevention could be associated with a reduction in the incidence of fractures, and with a better functional recovery following hip fracture. Fall prevention campaigns as well as advice on healthy and active ageing have contributed to the reduction in the incidence of hip fractures. The inclusion in care plans for geriatric patients with hip fracture of both nutritional assessments and the treatment of malnutrition could contribute to a better functional recovery and a reduction of mortality.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6643/10/5/555/s1, Table S1: Results of quality assessment of the observational included studies, Table S2: Results of quality assessment of included intervention studies.

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Supplementary Table S1. Results of quality assessment of the observational included studies

Year	Author	CK1	CK2	CK3	CK4	CK5	CK6	CK7	CK8	CK9	CK10	CK11	CK12	CK13	CK14	Quality
1990	Mansel	N	N	Y	NR	NR	N	N	NA	NA	NA	Y	NA	Y	N	Poor
1999	Maffulli	N	Y	Y	Y	NR	N	Y	N	N	NA	Y	NR	Y	N	Poor
2000	Murphy	Y	N	NR	NR	N	N	N	NA	N	NA	N	NR	Y	N	Poor
2001	Lumbers	Y	N	NR	Y	Y	N	Y	NA	NA	NA	Y	NR	Y	N	Poor
2006	Nematy	N	N	NR	NR	N	N	N	NA	NA	NA	Y	NR	NA	N	Poor
2010	Perez	Y	Y	NR	Y	N	N	N	NA	NA	NA	Y	NR	NA	N	Poor
2011	Perez	Y	Y	NR	Y	N	N	N	NA	NA	NA	Y	NR	NA	N	Poor
2012	Korem-Hakim	Y	Y	Y	Y	N	N	Y	NA	Y	NA	Y	Y	Y	N	Good
2013	Villani	Y	N	NR	N	N	N	N	NA	N	NA	Y	NR	NA	N	Poor
2014	Bell	Y	Y	Y	Y	N	N	Y	NA	N	NA	Y	NR	NA	Y	Fair
2005	Formiga	Y	Y	NR	Y	N	Y	Y	NA	Y	NA	N	NR	NA	N	Poor
2007	Montero	Y	Y	Y	Y	Y	Y	Y	NA	Y	NA	N	NR	Y	Y	Good
2009	Baumgarten	Y	N	NR	N	N	Y	Y	NA	Y	NA	Y	NR	NR	N	Poor
2010	Miyanishi	Y	N	Y	Y	N	Y	Y	NA	Y	NA	Y	NR	Y	N	Good
2011	Garcia Casanova	Y	Y	Y	Y	N	Y	Y	NA	N	NA	Y	N	N	N	Fair
2012	Schaller	Y	Y	Y	Y	N	Y	Y	NA	Y	NA	Y	NR	Y	Y	Good
2013	Gumieiro	Y	Y	NR	Y	Y	Y	Y	NA	Y	NA	Y	NR	Y	Y	Good
2014	Drevet	Y	N	N	Y	N	Y	Y	NA	Y	NA	N	N	N	N	Poor
2015	Goisser	Y	Y	Y	Y	N	Y	Y	NA	Y	NA	Y	NR	Y	N	Good
2016	Cenzer	Y	Y	Y	Y	NA	Y	Y	NA	Y	NA	Y	N	Y	Y	Good
2017	Bohl	Y	Y	Y	Y	N	Y	Y	NA	Y	NA	Y	NR	Y	Y	Good
2017	Helminen	Y	Y	Y	Y	N	Y	Y	NA	Y	NA	Y	NR	Y	Y	Good
2017	Mazzola	Y	Y	Y	Y	N	Y	Y	NA	Y	NA	Y	NR	Y	Y	Good
2017	Inoue	Y	N	Y	Y	N	Y	Y	NA	Y	NA	Y	NR	Y	N	Good
2016	Flodin	Y	N	Y	Y	N	Y	Y	NA	Y	NA	Y	NR	Y	Y	Good
2016	Uriz	Y	Y	Y	Y	N	Y	Y	NA	Y	NA	Y	NR	Y	Y	Good

Quality of included studies was assessed using the National Institutes of Health (NIH) Quality Assessment tool for Observational Cohort and Cross-Sectional Studies (https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort). CK 1. Was the research question or objective in this paper clearly stated? CK 2. Was the study population clearly specified and defined? CK 3. Was the participation rate of eligible persons at least 50%? CK 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? CK 5. Was a sample size justification, power description, or variance and effect estimates provided? CK 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? CK 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? CK 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? CK 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? CK 10. Was the exposure(s) assessed more than once over time? CK 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? CK 12. Were the outcome assessors blinded to the exposure status of participants? CK 13. Was loss to follow-up after baseline 20% or less? CK 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? CK, check list; CD, cannot be determined; NA, not applicable; NR, not reported; N, no; Y, yes.

Supplementary Table S2. Results of quality assessment of included intervention studies

Year	Author	CK1	CK2	CK3	CK4	CK5	CK6	CK7	CK8	CK9	CK10	CK11	CK12	CK13	CK14	Quality
1998	Schürch	Y	Y	NR	Y	NR	Y	N	Y	NR	NR	Y	NR	NR	N	Poor
2000	Espaulella	Y	Y	Y	Y	NR	Y	Y	N	NR	NR	Y	N	N	N	Fair
2003	Bruce	N	N	N	N	N	Y	NR	NR	NR	NR	Y	N	N	NR	Good
2003	Houwing	Y	NR	NR	Y	NR	Y	Y	Y	N	NR	Y	N	Y	Y	Good
2004	Tidermark	Y	Y	Y	N	NR	Y	Y	Y	Y	Y	Y	NR	N	N	Good
2005	Eneroth	Y	Y	Y	N	N	N	Y	Y	NR	NA	Y	NR	N	Y	Fair
2006	Duncan	Y	NR	NR	N	NR	Y	NR	NR	NR	NA	Y	Y	N	N	Poor
2007	Hommel	N	NA	NA	N	N	N	NR	NR	N	NA	Y	N	N	NA	Poor
2010	Botella Carretero	Y	Y	Y	N	N	Y	Y	Y	N	NA	Y	Y	N	NA	Good
2011	Fabian	Y	NR	NR	N	NR	NR	NR	NR	NR	Y	Y	N	N	N	Poor
2011	Hoekstra	N	NA	NA	N	N	Y	Y	Y	NR	Y	Y	N	N	N	Poor
2013	Li	Y	NR	NR	N	NR	Y	N	Y	NR	NR	Y	NR	N	Y	Poor
2013	Wyers	Y	Y	N	N	NR	Y	Y	Y	NR	NA	Y	N	N	N	Poor
2013	Myint	Y	Y	Y	N	NR	Y	Y	Y	Y	Y	Y	Y	N	N	Good
2014	Anbar	Y	Y	Y	N	NR	Y	Y	Y	NR	NR	Y	Y	N	NA	Good
2016	Ekinci	Y	Y	N	N	N	Y	Y	Y	NR	Y	Y	Y	N	N	Good
2017	Malafarina	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	N	N	N	Good

Quality of included studies was assessed using the National Institutes of Health (NIH) Quality Assessment of Controlled Intervention Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). **CK 1.** Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT? **CK 2.** Was the method of randomization adequate (i.e., use of randomly generated assignment)? **CK 3.** Was the treatment allocation concealed (so that assignments could not be predicted)? **CK 4.** Were study participants and providers blinded to treatment group assignment? **CK 5.** Were the people assessing the outcomes blinded to the participants' group assignments? **CK 6.** Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)? **CK 7.** Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment? **CK 8.** Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower? **CK 9.** Was there high adherence to the intervention protocols for each treatment group? **CK 10.** Were other interventions avoided or similar in the groups

(e.g., similar background treatments)? **CK 11.** Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants? **CK 12.** Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power? **CK 13.** Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)? **CK 14.** Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?

4.2 CAPÍTULO 2

Effectiveness of Nutritional Supplementation on Sarcopenia and Recovery in Hip Fracture Patients. A Multi-Centre Randomized Trial.

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Effectiveness of nutritional supplementation on sarcopenia and recovery in hip fracture patients. A multi-centre randomized trial

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ABSTRACT

Background and objectives: Functional deterioration and reduced mobility in elderly patients with a hip fracture are associated with a loss of both muscle mass and function (sarcopenia). The aim of this study was to assess whether oral nutritional supplementation (ONS) improves muscle mass and nutritional markers (BMI, proteins) in elderly patients with hip fracture.

Methods: Patients aged 65 years and over with hip fractures admitted to either of two rehabilitation facilities were included. Patients with diabetes, with Barthel index scores < 40 prior to the fracture or with pathological fractures were excluded. A random-numbers generator was used to randomly allocate patients to the intervention group (IG) or the control group (CG). Those in the IG received a standard diet plus ONS in the form of two bottles a day of β-hydroxy-β-methylbutyrate (HMB), while those in the CG received a standard diet only. The intervention was not blinded.

In order to assess changes in body mass index (BMI), anthropometric parameters were recorded at both admission and discharge. Patients' functional situation was evaluated using the Barthel index (BI) and the Functional Ambulation Categories (FAC) score. Muscle mass was assessed using bioelectrical impedance analysis, which allowed us to calculate appendicular lean mass (aLM). The outcome variable was the difference between aLM upon discharge, minus aLM upon admission (Δ-aLM).

Results: Of the 107 randomised patients (IG n55, CG n52), 49 finished the study in the IG and 43 in the CG. BMI and aLM were stable in IG patients, whilst these parametres decreased in the CG. A significant difference was observed between the two groups ($p < 0.001$, and $p = 0.020$ respectively). The predictive factors for Δ-aLM were ONS ($p = 0.006$), FAC prior to fracture ($p < 0.001$) and BI prior to fracture ($p = 0.007$).

The concentration of proteins ($p = 0.007$) and vitamin D (p.001) had increased more in the IG than in the CG.

Conclusion: A diet enriched in HMB improves muscle mass, prevents the onset of sarcopenia and is associated with functional improvement in elderly patients with hip fractures. Orally administered nutritional supplements can help to prevent the onset of sarcopenic obesity.

Trial registration: www.clinicaltrials.gov identifier: NCT01404195, registered 22 July 2011, HYPERPROTGER Study.

1. Introduction

Hip fractures represent 14% of all fractures but they amount to 72% of all cost associated with fractures [1]. Maintaining functional independence is of paramount importance in the lives of patients with fractured hips and rehabilitation centres play a special role here [2,3].

Approximately 40% of elderly people with a fracture do not recover their previous functional status [4]. Functional loss is associated with institutionalization and increases mortality [5]. Bed confinement and the reduced mobility of hospitalized elderly patients are associated with

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loss of muscle mass and muscle function (sarcopenia) and loss of bone mineral density from the 10th day and up to 2 months after the fracture [6,7]. The prevalence of sarcopenia in elderly patients with hip fractures is up to 54%, and it is higher in men than in women [8]. The postoperative standard diet has been regarded as unsatisfactory to prevent weight loss in trauma patients [9,10], while physical rehabilitation and nutritional supplementation have proven to be effective strategies to reduce the loss of muscle mass in older people [11,12].

Elderly patients with a hip fracture who are well nourished are more independent in activities of daily living (ADL), while malnourished patients show worse functional recovery [13] and gait recovery. [14,15]

β-hydroxy-β-methylbutyrate (HMB) is a leucine metabolite that has been shown to improve the synthesis and to reduce the degradation of muscle proteins [16]. The endogenous output of HMB reduces with age and its levels are associated with the loss of appendicular lean mass and hand grip strength [17]. Supplementation with 3 g of HMB prevents the muscle loss associated with bed confinement [17]. Branched chain amino acids (e.g. leucine) are responsible for the activation of muscle metabolism by stimulating the mammalian target of rapamycin (mTOR) [18].

Prior studies have assessed the effects of oral nutritional supplementation only on issues such as weight [19], complications [20], and hospital stay [21].

The hypothesis of the present study is that a nutritional supplement enriched with HMB, calcium (Ca) and 25-hydroxy vitamin D (25(OH)D) taken during rehabilitation therapy will improves muscle mass and thereby functional recovery.

The purpose of this study is to assess whether oral nutritional supplementation (ONS) improves muscle mass and nutritional markers (BMI, proteins) in elderly patients with a hip fracture.

2. Methods

2.1. Study design and participants

Both the patient selection criteria and the study methodology have been previously described [22]. In a departure from the original protocol, a second recruitment centre was included, but otherwise none of the inclusion and exclusion criteria were modified. In short, the Hyperprotein Nutritional Intervention in Elderly Patients With Hip Fracture and Sarcopenia (HIPERPROT-GER) study is a multicentre randomized open-label study. Inclusion criteria were age ≥65, and a diagnosis of hip fracture. The study was carried out in two post-acute rehabilitation centres: 1) Hospital San Juan de Dios, Pamplona, Spain (2012 and 2013) and 2) Hospital Viamed Valvanera, Logroño, Spain (2014 and 2015). Exclusion criteria were diabetes (because the ONS is not suitable for diabetic patients), established disabilities, defined by a Barthel index score < 40 prior to the fracture, tumour treated with chemotherapy or radiotherapy, pathological fractures and high-impact fractures (car crashes).

This study was approved by the Comunidad Foral de Navarra Clinical Research Ethics Committee (62/2011) and was conducted following the Good Clinical Practice Standards set by the European Union and the Helsinki Declaration. Written informed consent was provided by all patients or their legal representatives.

2.2. Description of rehabilitation centres

In Navarra, there are some 600 hip fractures every year and a further 300 occur in a year in La Rioja [2]. Almost one-third of these patients with hip fractures are referred to either of two post-acute rehabilitation centres: Hospital San Juan de Dios (Navarra) and Hospital Viamed Valvanera (La Rioja). Reasons for referral are the high clinical complexity of patients due to their high comorbidity and the presence of complications at admission, or patients having only a partial response to the rehabilitation therapy provided in the trauma units. We recorded the variables for this study within the first 72 h after admission to the rehabilitation units (following randomisation) and again 48 h before discharge.

We recorded the type of fracture, the type of surgery and the duration of stay at the trauma unit and at the rehabilitation unit. We also recorded post-operative complications.

2.3. Nutritional intervention

Individuals included were randomized to either the intervention group (IG) or the control group (CG). The IG received a standard diet plus oral nutritional supplementation during their stay in the rehabilitation units, while the CG received a standard diet. The intervention did not change the length of stay. Patients were discharged from the rehabilitation units when the responsible physician considered that they had no more need of rehabilitation.

The nutritional characteristics of the standard diet are: 1500 kcal, 23.3% protein (87.4 g/day), 35.5% fat (59.3 g/day) and 41.2% carbohydrates (154.8 g/day). In addition, patients in the IG received two bottles a day (one in the morning and one in the afternoon) of pre-prepared oral liquid nutritional supplementation (220 ml x 2, total: 660 kcal) (Ensure® Plus Advance, Abbott Laboratorios S.A.) with the following nutritional characteristics: 1.5 kcal/mL, 24% protein (9.1 g/100 ml), 29% fat (5 g/100 ml) and 46% carbohydrates (16.8 g/100 ml). The supplement was enriched with CaHMB 0.7 g/100 ml, 25(OH)D 227 IU/100 ml and 227 mg/100 ml of calcium.

2.4. Sarcopenia diagnosis and study of body composition

The test to assess walking speed was performed by an experienced and trained physiotherapist (PT) over a distance of 4 m. We considered values < 0.8 m/s to be reduced walking speed (slowness). Grip strength of both hands was measured using a JAMAR digital dynamometer (Akern, Italy) based on the original protocol [23]; measurement that was taken twice with a 60-s break between the two measurements. We used the better of the two results. We considered values < 20 kg in women and < 30 kg in men to indicate weakness.

Muscle endurance was determined as fatigue resistance (FR), i.e. the time in seconds that each patient kept the dynamometer from points of maximum strength to less than 50% of that value. Grip work (GW) was calculated using the following formula: GW = (maximum strength x 0.75) x FR [24]. GW was divided by weight in kilograms to calculate the Grip Work Index.

For the Bioelectrical Impedance Analysis (BIA) we used a single-frequency tetrapolar BIA-101 device (Akern, Italy). BIA was carried out with the patient in the supine position on a nonconductive surface, in slight upper extremity adduction and with the lower limbs slightly separated, while the electrodes were placed on the side unaffected by the fracture. The BIA values were used in the equation described by Sergi et al. for predicting muscle mass (MM) [25]:

$$MM = -3.964 + 0.227 \times height^2/Resistance + 0.095 \times weight + 1.384 \times sex + 0.064 \times Reactance.$$

We measured height in centimetres, resistance and reactance in ohms; male sex = 1 and female sex = 0, and weight in kg. MM was converted to appendicular lean mass (aLM) using model 1 described by Kim et al. [26].

$$aLM = (Total\ body\ skeletal\ muscle\ mass)/1.19 + 1.65$$

Low aLM was defined as aLM ≤ 5.67 kg/m^2 for women, and aLM ≤ 7.25 kg/m^2 for men. We used delta-aLM (Δ-aLM) for the outcome variable, calculating the difference as aLM upon discharge minus aLM on admission. Sarcopenia was defined in accordance with the definition proposed by the European Working Group on Sarcopenia in Older

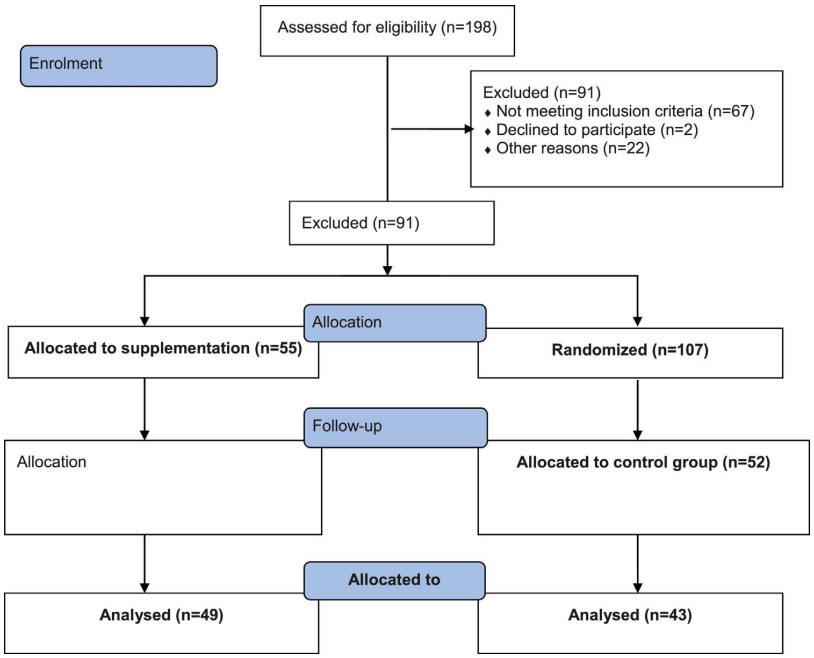

Fig. 1. CONSORT diagram of participants through the trial.a: patients who after beginning the study decided that they no longer wished to participate.b: patients who withdrew from the study after being referred to an acute care hospital due to complications.c: patients excluded for lacking compliance with the treatment − taking less than 50% of the indicated oral nutritional supplementation.d: patients whose intake was very small, for whom nutritional treatment wasindicated and who were therefore excluded from the study.

People (EWGSOP) [27].

2.5. Clinical characteristics

Weight was measured (in kg) by weighing patients on a wheel chair. Height (in cm) was measured with patients in the supine position. Body mass index (BMI) (weight/height^2) was calculated accordingly.

Nutritional assessment was carried out by a nutritionist who used the Mini Nutritional Assessment − Short Form (MNA-SF) based on the original classification: 12–14 points = well nourished; 8–11 points = -risk of malnutrition; and 0–7 points = malnutrition [28].

For the assessment of activities of daily living (ADL), an experienced trained PT used the Barthel index [29] (on which scores range from 0 points, indicating total dependency, to 100 points, indicating total self-sufficiency) and scores prior to the fracture (determined retrospectively via interview) and at discharge were taken into account.

The PT measured self-sufficiency while walking using the Functional Ambulation Categories (FAC) score, which ranges from 0, nonfunctional walking, to 5, independent walking on an even surface and stairs [30].

For the cognitive assessment the Mini Mental State Examination (MMSE) was used [31]. Comorbidity was defined on the basis of the Charlson index [32].

2.6. Blood tests and laboratory assessment

One blood test was carried out to record blood count and kidney function, total proteins, albumin, transthyretine, and 25(OH)D levels. Lipid metabolism was assessed by measuring the concentration of total cholesterol and triglycerides. For the study of glycemic metabolism, both the glycemic levels and the blood concentration of insulin were measured using the Homeostasis Model Assessment (HOMA) index to calculate insulin-resistance, using the original formula: HOMA = Insulin (mcU/mL) x [glycemia (mmol/l)/22.5] [33].

We measured the concentration of C-reactive protein (CRP) and blood concentrations of interleukin-1 (IL-1), interleukin −6 (IL-6) and tumour necrosis factor-alpha (TNF-α) in order to study the inflammatory state.

All tests took place in the morning after 8 h of fasting. Tests were repeated 72 h before discharge.

2.7. Social assessment

A social worker took the social history of patients, including their marital status, usual address and level of education, and used the Gijón scale [34] to score the patient's social-familial assessment, including family and economic situation, home, social relations and social support. Based on their Gijón scale score, patients were categorized as follows: low or normal social risk, for patients with values < 10; intermediate social risk, for patients with scores between 10 and 16; and high social risk for patients with scores ≥17. Destination upon discharge was recorded.

2.8. Rehabilitation therapy

Rehabilitation therapy comprised two distinct parts. The first part took place in the hospital ward (nursing staff and occupational therapist) and was based on moving patients early using technical aids (canes, crutches or walker), and rehabilitation of activities of daily living. The second part (physical therapy) took place at the hospital gym (PTs) and included exercises to strengthen the lower limbs, balance exercises and walking re-training in individual or group 50-minunte sessions, once a day five days a week (Monday to Friday).

2.9. Statistical analysis

Patient randomization was carried out with a random number generator, using R software and the 'runif' function, using a central

Table 1
Basal characteristics and discharge destination.

Variables	All patients n = 107	Control group n = 43	Intervention group n = 49	Drop-out n = 15
Age, years	85.4 ± 6.3	84.7 ± 6.3	85.7 ± 6.5	86.7 ± 5.7
Men	83.4 ± 7.7	82.5 ± 8.1	83.1 ± 7.4	86.5 ± 9.0
Women	86.1 ± 5.6	85.2 ± 5.8	87.0 ± 5.7	86.7 ± 4.7
Female	79 (73.8%)	35 (81.4%)	33 (67.3%)	9 (69.2%)
Gijon scale	9 (8–11)	9 (8–10)	10 (8–12)	9 (7–10)
Schooling				
Primary	99 (92.5%)	41 (95.3%)	43 (87.8%)	15 (100%)
Marital status				
Married	33 (30.8%)	16 (35.6%)	13 (26.5%)	4 (30.8%)
Single	16 (15.0%)	6 (13.3%)	10 (20.4%)	0
Widow	56 (52.3%)	20 (46.5%)	25 (51.0%)	11 (69.2%)
Social support				
Lives alone	35 (33%)	13 (33.3%)	18 (36.7%)	4 (15.4%)
Spouse	30 (28%)	13 (28.9%)	13 (26.5%)	4 (30.8%)
Son/daughter	28 (26.2%)	13 (28.9%)	8 (16.3%)	7 (53.8%)
Caregiver	5 (4.7%)	2 (4.4%)	3 (6.1%)	0
Other	7 (6.5%)	1 (2.2%)	6 (12.2%)	0
Type of fracture				
Intracapsular	46 (43%)	18 (41.9%)	24 (49%)	4 (26.7%)
Extracapsular	61 (57%)	25 (58.1%)	25 (51%)	11 (73.3%)
Surgical method				
Prosthetic replacement	32 (29.9%)	13 (30.2%)	16 (32.7%)	3 (20.0%)
Internal fixation	75 (70.1%)	30 (69.8%)	33 (67.3%)	12 (80.0%)
Time to surgery (d)	2.9 ± 2.0	3.1 ± 2.0	2.8 ± 4.1	2.9 ± 2.2
Length of Stay				
Orthopaedic wards[a] (d)	10.3 ± 3.8	10.1 ± 3.9	10.4 ± 4.0	10.7 ± 2.9
Rehabilitation units[b] (d)	42.3 ± 20.9	42.5 ± 19.4	41.9 ± 20.5	43.1 ± 27.0
Complication n (%)				
Anaemia Transfused	60 (56.1%)	21 (58.8%)	30 (61.2%)	9 (60.0%)
Delirium	26 (24.3%)	10 (23.3%)	14 (28.6%)	2 (13.3%)
Urinary Infection	5 (4.7%)	2 (4.7%)	3 (6.1%)	0
Urinary Retention	10 (9.3%)	1 (2.3%)	5 (10.2%)	3 (20.0%)
Respiratory Infection	7 (6.5%)	2 (4.7%)	5 (10.2%)	0
Heart Failure	5 (4.7%)	3 (7.0%)	1 (2%)	1 (6.7%)
Pressure Ulcers	1 (0.9%)	1 (2.3%)	0	0
No weight bearing	15 (14%)	7 (16.3%)	8 (16.3%)	0
MMSE	24 (19.5–27.5)	24 (21–28)	24 (19–26)	22 (19.5–26)
FAC Previous	5 (4–5)	5 (4–5)	4 (4–5)	5 (4–5)
FAC at discharge	3 (3–4)	3 (3–4)	3 (3–4)	–
Barthel Index				
Previous	95 (80–100)	90 (77.5–100)	95 (75–100)	100 (90–100)
At discharge	65 (40–85)	65 (40–82.5)	65 (30–90)	–
MNA-SF (n 71)	10 (8–12)	9 (8–12)	11 (9–12)	7 (7–12)
Discharge destination				
Home	84 (78.5%)	38 (88.4%)	40 (81.6%)	–
Nursing-home	9 (8.4%)	4 (9.3%)	4 (8.2%)	–

Results are expressed as Median (IQR), Mean ± SD or number of individuals (percentage).
FAC: Functional Ambulation Categories:
MMSE: Mini Mental State Examination; MNA-SF: Mini Nutritional Assessment-Short Form.
[a] Stay from ER admission to discharge from the acute orthopaedic wards.
[b] Length of stay from admission to discharge from the rehabilitation units (study time).

computer system. The principal investigator was responsible for randomization. Using the generated randomization list, the principal investigator assigned patients to one of two groups (intervention or control group). The intervention was not blinded. Quantitative variables were expressed as mean ± standard deviation (for normally distributed variables), and median and inter-quartile interval for non-normally distributed variables. The Shapiro-Wilk test was used to assess the normal distribution of the included variables. The Student *t*-test, and the Mann-Whitney *U* test were used for comparisons between variables. Categorical variables were expressed as number of subjects (percentage); and comparisons were done using the chi-square test.

The Student *t*-test was used for comparison within each group. The ANCOVA method was used in order to compare the results of both groups, for quantitative variables, correcting the analysis for the basal values. For the multivariate study, adjusted for possible confounding factors, we used the stepwise variable selection method. It was not possible to carry out an assessment with intention to treat groups, as designed in the original protocol, because it was not possible to record outcome variables upon discharge for patients who were referred to other hospitals for medical complications. The statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS), version 20.0 (IBM Corporation, Chicago, IL).

3. Results

During the study period, 198 patients with hip fractures admitted to the centres were screened for inclusion in the study and 107 (52%) patients were randomised (Fig. 1). Compared with participants, excluded patients (n 91, 72% women, mean age 85.7 ± 6.5) presented worse functional status (previous BI, $p < 0.001$), worse cognitive status (MMSE, $p < 0.001$) and a higher prosthetic replacement percentage (47%, $p = 0.008$), whilst no significant differences were found in the rest of variables assessed (e.g. sex, age, comorbidity, etc.).

The baseline characteristics of the included patients (age

Table 2
Nutritional and biochemical measurements.

Variables	Control group (CG)		Intervention group (IG)		p value
	Admission	Discharge	Admission	Discharge	
Height (m)	**n 45**		**n 49**		
	1.6 ± 0.1		1.6 ± 0.1		
Weight (Kg)		**n 44**		**n 42**	**< 0.001**
	63.2 ± 14.7	59.9 ± 14.1	62.7 ± 12.9	62.5 ± 12.7	
BMI (Kg/m^2)					**< 0.001**
	26.0 ± 5.4	24.7 ± 5.1	24.9 ± 4.4	24.6 ± 4.6	
Haemoglobin (g/dL)		**n 43**		**n 43**	**.240**
	10.5 ± 1.2	12.0 ± 1.2	10.6 ± 1.2	11.6 ± 1.0	
Total protein (g/dL)				**n 42**	**.007**
	5.7 ± 0.5	6.1 ± 0.5	5.8 ± 0.5	6.5 ± 0.5	
Albumin (g/dL)					**.118**
	3.0 ± 0.4	3.4 ± 0.4	3.1 ± 0.4	3.6 ± 0.3	
Prealbumin (mg/dL)		**n 38**		**n 35**	**.037**
	17.1 ± 4.8	19.8 ± 5.2	16.0 ± 5.9	21.9 ± 5.1	
Creatinin (mg/dL)	**n 44**		**n 49**		**.948**
	0.9 ± 0.3	0.9 ± 0.3	1.0 ± 0.4	0.9 ± 0.4	
Total Cholesterol (mg/dL)	**n 44**	**n 43**	**n 49**	**n 39**	**.336**
	169.5 ± 35.7	176.9 ± 39.6	155.0 ± 37.4	168.9 ± 35.5	
Triglycerides (mg/dL)		**n 42**			**.604**
	127.1 ± 45.4	125.3 ± 50.9	130.8 ± 53.5	131.1 ± 48.5	
25(OH)D (ng/mL)	**n 40**		**n 37**		**< 0.001**
	9.2 (5–14)	12.2 (7–19.6)	9 (7–12)	20.8 (16–30)	
CRP (mg/L)	**n 42**	**n 38**	**n 48**	**n 37**	**< 0.001**
	24 (7.2–36)	6.5 (2.2–10)	20.3 (4.5–35)	4 (1.8–11)	
IL-1 (pg/mL)	**n 36**		**n 35**		**.642**
	1.1 (0.4–5.8)	0.5 (0.4–4.8)	0.4 (0.4–4.5)	0.9 (0.4–3.6)	
IL-6 (pg/mL)					**.272**
	13.9 (8.6–21.1)	5.6 (2.5–8.4)	19.4 (13–24.1)	6.8 (4.2–9.2)	
TNF-alfa (pg/mL)					**.180**
	11.8 (6.8–18.5)	9.5 (5–14)	9.9 (5.4–14.8)	11.3 (7.7–15.1)	
Glycemia (mg/dL)	**n 45**	**n 40**	**n 49**	**n 43**	**.238**
	94.4 ± 11.1	88.5 ± 12.2	94.9 ± 12.3	91.9 ± 14.1	
Insulin (mcU/mL)	**n 45**	**n 39**	**n 48**	**n 36**	**.412**
	7.6 ± 5.2	6.9 ± 5.9	7.1 ± 8.1	8.3 ± 8.3	
HOMA					**.346**
	1.9 ± 1.4	1.6 ± 1.6	1.7 ± 2.2	2.1 ± 2.7	

Results are expressed as Median (IQR), Mean ± SD.
p Value: for parametric variables is the result of the ANCOVA test, the differences in the variables between the groups at discharge corrected by values and readings at admission. For non-parametric variables is the result of U-Mann Whitney test.
n = number of patients with all the information for each variable.
BMI: Body Mass Index, 25(OH)D: 25-Hydroxy-Vitamin D, CRP: C-Reactive Protein, IL-6: Interleukin-6, IL-1: interleukin-1, TNF-alpha: Tumour Necrosis Factor-alpha, HOMA: Homeostasis Model Assessment.
Bold values represent the number of patients with all the information for each variable.

85.4 ± 6.3, 74% female) are shown in Table 1. The average length of stay in the rehabilitation units was 42.3 ± 20.9 days (42.5 ± 19.4 days for the control group, and 41.9 ± 20.5 days for the intervention group) (Table 1). Almost all patients came from their own home (n 105), with good baseline functional status (prior BI 90 CI95% 80–100) and cognitive status (MMSE 24 CI95% 19.5–27.5).

During admission 6 patients died (5.6%). They were older patients (92.0 ± 3.6 years old, p = 0.009) with longer average stays in the trauma unit (14.8 ± 7.3 days, p = 0.003) but without any other differences with respect to the rest of the sample.

All of the subjects in the intervention group took more than 80% of the prescribed oral nutritional supplement, demonstrating good adherence to treatment.

3.1. Nutritional status

The MNA-SF was conducted on 71 patients and most of them (n 47, 66%) showed some degree of malnutrition (47.9% at risk of malnutrition and 18.3% with malnutrition).

More weight loss was observed in the control group than in the intervention group (p < 0.001) (Table 2 and Fig. 2 panel A). The results of the multivariate analysis show that the two predictive factors for BMI upon discharge were: 1) BMI upon admission, and 2) oral nutritional supplementation (Table 3). The ANCOVA, corrected for basal values, shows that in the intervention group total protein values, transthyretin and 25(OH)D upon discharge were significantly higher than in the control group (p = 0.007, p = 0.037 and p < 0.001, respectively) (Table 2).

The blood concentration of 25(OH)D increased significantly in the intervention group compared with the control group (p = 0.005) (Table 2). Only 5% of the individuals in the intervention group and 41% of the individuals in the control group had 25(OH)D values < 10 ng/mL at discharge.

3.2. Inflammatory markers

Fifty-seven per cent of the individuals in the intervention group and 43% of the individuals in the control group had CRP values ≤5 (p = 0.084) at discharge.

Also, a decrease in the levels of IL-1, IL-6 and TNF-alpha was reported − and this was more accentuated in the intervention group (Table 2).

In the intervention group there was a slight increase in the concentration of insulin and HOMA values − but this was non-

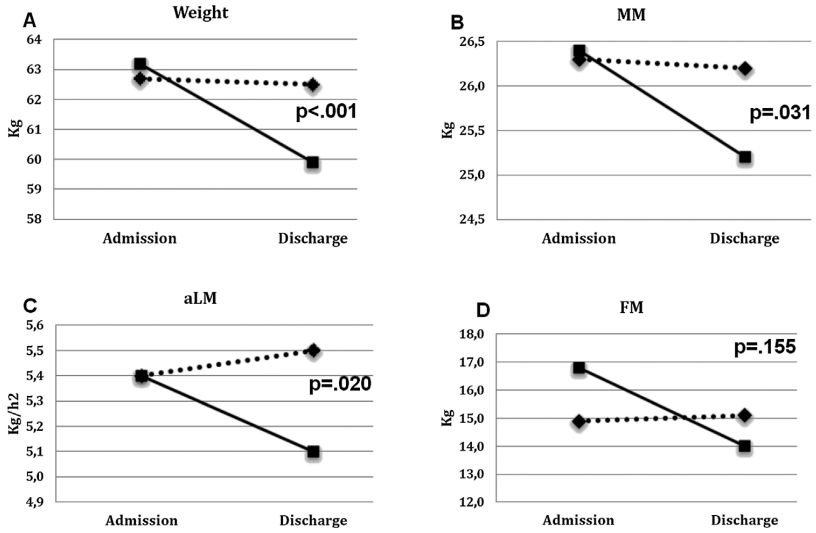

Fig. 2. Body composition study. Panel A: loss of weight among individuals in the control group (solid line), while in the intervention group weight was gained (dotted linen). Panel B and C: increases in muscle mass (MM) and in appendicular lean mass (aLM) in the IG (dotted line), compared with the CG (solid line), in which a decrease in both values was observed. Panel D: fat mass (FM) in both the IG (dotted line), and in the CG (solid line).

Table 3
Multivariable Models of Predisposing Factors.

	Adjusted Odds Ratio (95% Confidence Interval)		
	Δ-aLM†	BMI at discharge§	Barthel index at discharge‡
ONS	−0.35 (−0.60 to −0.11	0.79 (0.13–1.45)	–
Previous BI	−0.02 (−0.03–−0.01)	–	–
Previous FAC	0.40 (0.18–0.61)	–	12.20 (6.00–18.40)
BMI at admission	–	0.95 (0.88–1.02)	–
Age	–	–	−1.37 (−2.31 to −0.43)
Charlson index	–	–	−4.14 (−7.69 to −0.59)
MMSE	–	–	0.82 (0.03–1.61)

BI: Barthel index; BMI: Body Mass Index; Δ-aLM: delta-aLM (appendicular Lean Mass) difference between aLM upon discharge minus aLM on admission; FAC: Functional Ambulation Categories; MMSE: Mini Mentas State Examination; ONS: oral nutritional supplementation.
Adjusted Univariable Factors: † sex, age, ONS, previous BI, MMSE, previous FAC. § sex, age, ONS, previous BI, MMSE, previous FAC, admission BMI, admission total protein (g/dL), Charlson index, aLM at admission. ‡ sex, age, ONS, previous BI, MMSE, previous FAC, admission BMI, admission total protein (g/dL), Charlson index and rehabilitation length of stay.

significant compared with the control group.

3.3. Sarcopenia markers and body composition study

Table 4 shows the mean ± SD of the sarcopenia diagnostic markers (gait speed, hand grip strength, and body composition) at admission and discharge.

Gait speed was available only on discharge because on admission patients were unable to walk. No differences between the groups were observed.

Despite no differences having been found between the groups in terms of strength, measured with the GWI, an increase in GWI was observed in the intervention group, which did no occur in the control group.

As regards the muscle mass indices, a reduction in aLM was observed in the control group, whereas the values remained stable in the intervention group. The difference between values upon discharge, corrected to take into account basal values, was statistically significant ($p = 0.020$) (Table 4). We found three factors that predicted Δ-aLM: 1) oral nutritional supplementation, 2) previous Barthel index score, and 3) the previous FAC score (Table 3).

We used the criteria proposed by the EWGSOP to diagnose sarcopenia at discharge. Among the entire population, 24 (28%) individuals did not have sarcopenia, and 62 (72%) had sarcopenia.

3.4. Activities of daily living

The mean Barthel index at discharge was 61.9 ± 28.6.

A positive effect of oral nutritional supplementation on ADL recovery was reported. The recovery of ADL was more common in the intervention group (68%) than in the control group (59%) ($p = 0.261$). We found four predictive factors for the Barthel index score upon discharge: 1) FAC score prior to fracture; 2) age; 3) the Charlson index score; and 4) the MMSE score (Table 3).

4. Discussion

To our knowledge, this is the first study to assess the effects of an oral nutritional HMB supplement with in elderly patients with hip fractures admitted to rehabilitation facilities. This study demonstrates that patients who receive nutritional oral supplementation suffer fewer complications and less sarcopenia, and – conversely − undergo an improvement in body composition and have a better functional and nutritional status upon being discharged. Former studies showed the benefits of oral nutritional supplementation on weight [19] and complications [20].

The prevalence of sarcopenia was greater in the present study than is reported in studies conducted in the community (4–25%) [35], hospitals (25%) [36], or nursing homes (32%) [37]. Several factors may have influenced this. Firstly, the high degree of heterogeneity in the definition and the measurement of sarcopenia makes the results of different studies hard to compare [38]. Secondly, the average age of our

Table 4
Sarcopenia parameters, hand grip strength, gait speed and bioimpedance measurements.

Variables	Control group (CG)		Intervention group (IG)		p value
	Admission n 45	Discharge n 38	Admission n 49	Discharge n 36	
Gait-speed (m/s)	–	0.4 ± 0.3	–	0.4 ± 0.3	0.367
Hand-grip (Kg)	13.8 ± 6.2	14.6 ± 6.7	15.6 ± 7.6	16.8 ± 8.8	0.752
Grip work index	4.4 ± 3.7	6.3 ± 4.4	4.1 ± 2.7	6.8 ± 5.4	0.188
MM by Sergi et al. [24]	4.5 ± 1.6	4.1 ± 1.7	4.5 ± 1.4	4.6 ± 1.4	0.020
aLM by Sergi et al. [24]	5.4 ± 1.4	5.1 ± 1.4	5.4 ± 1.1	5.5 ± 1.2	0.020
SMM	23.6 ± 10.0	22.7 ± 7.9	25.5 ± 9.9	24.3 ± 8.6	0.368
ASMM	18.1 ± 5.6	17.1 ± 4.6	18.8 ± 5.3	18.1 ± 4.8	0.026
MM	26.4 ± 7.0	25.2 ± 5.3	26.3 ± 7.3	26.2 ± 6.4	0.031
FFM	46.8 ± 9.5	45.4 ± 7.7	47.8 ± 9.5	47.1 ± 8.2	0.016
FM	16.8 ± 13.4	14.0 ± 10.9	14.9 ± 10.6	15.1 ± 9.7	0.155

Results are expressed as Mean ± SD. p value = result of the t-Student test, of the result of the differences between values upon discharge minus values on admission.
aLM: appendicular lean mass, ASMM: appendicular skeletal muscle mass, FFM: fat free mass, FM: fatty mass, MM: muscle mass, SMM: Skeletal Muscle Mass.

patients (almost 86 years old) was greater than that in the earlier studies [36]. Thirdly, our study was conducted in rehabilitation centres to which the patients with most clinically complex conditions are admitted [39]. Lastly, in elderly patients with hip fractures the recovery of one of the diagnostic parameters of sarcopenia – gait – is slower than the recovery of other aspects of functional capacity (like dressing, continence, or eating) [40].

Yet despite the high prevalence of sarcopenia, 68% of the individuals in the intervention group recovered to the extent that their functional status matched what it had been before the fracture, which is a larger proportion than is reported in former studies without nutritional supplementation [5]. Several studies have shown the validity of BIA in assessing nutritional status, as well as measuring body composition in elderly patients with a hip fracture [41–43]. The novelty in this study is that it demonstrates how the observed increase in weight is due to a significant increase in muscle mass coupled with a non-significant change in fat mass. This research shows that hypercaloric and hyperproteic nutritional supplementation helps to preserve appendicular lean mass and can be effective in the treatment of sarcopenia. It would be interesting to conduct research into whether the decrease in the prevalence of sarcopenia and the better functional response in elderly patients with hip fractures is maintained over the long term.

In situations of fast or reduced intake compared with metabolic requirements, muscle can be viewed as the organism's "supermarket". When there is insufficient intake (as may happen in hospitalized elderly people) the body recovers necessary nutrients by metabolizing muscle tissue [44]. This study shows that when patients are given oral nutritional supplements their muscle mass increases and fat mass remains unchanged. In contrast, subjects in the control group lost muscle mass, developing a pattern known as sarcopenic obesity [45,46].

The low concentration of 25(OH)D is associated with a reduction in muscle mass and strength, and supplementation with 25(OH)D is effective in the prevention and management of frailty [47]. In this study we saw that the amount of 25(OH)D contained in the oral nutritional supplement was effective in restoring normal values of vitamin D in most patients treated.

The proinflammatory IL-6 cytokine is also known as myokine, since it is produced by muscle cells in response to regular physical exercise in the absence of muscle damage [48]. Yet despite the significant decrease in both groups in the concentration of IL-6 after admission, the persistence of relatively high values could be associated with the rehabilitation process and thus be considered a positive marker of muscle activation [49].

4.1. Limitations and strengths of the study

This study has a number of limitations. First, our patients received rehabilitation five days a week. It will be interesting to see whether participation in a programme of resistance exercises during patients' stay at a rehabilitation centre improves the functional results reported. Second, we could not do any follow-up of our patients after discharge to assess whether the benefits obtained were maintained. Third, the diagnostic criteria for sarcopenia proposed by the EWGSOP are difficult to apply in patients with hip fractures admitted to rehabilitation units, because most of the patients are unable to walk when they arrive. Despite this, the aforementioned criteria can be applied at the time of discharge from rehabilitation, whereby our research has shown a high prevalence of sarcopenia.

Yet despite these limitations, this research has some important strengths. Due to the characteristics of the patients included, we believe our study is representative of the geriatric population admitted to rehabilitation centres. The methodology used for this randomized multicentre study, whose protocol was registered, adds clinical significance to the results obtained.

5. Conclusions

In elderly patients with hip fractures, oral nutritional supplements with HMB improves muscle mass (sarcopenia), prevents weight loss and therefore the onset of malnutrition, and helps with functional recovery. ONS with HMB could be an effective intervention to reduce sarcopenia and malnutrition and could prevent the onset of disability secondary to hip fractures in elderly patients with hip fractures.

Contributors

VM was the principal investigator, wrote the study protocol, was involved in the training of the staff who took part in the study, conducted the statistical analysis and ultimately wrote this paper. This research is part of the VM's PhD project.

FU-O took part in the statistical analysis of the results and in the writing of the paper.

CM and JAM helped in the critical analysis of the findings, and in both the correction and the editing of the manuscript.

MAZ was the supervisor of the PhD project, and contributed to the critical analysis of findings and the writing and editing of this paper.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

This study was approved by the Comunidad Foral de Navarra Clinical Research Ethics Committee (62/2011) and was conducted following the Good Clinical Practice Standards set by the European Union and the Helsinki Declaration. Written informed consent was provided by all patients or their legal representatives.

Provenance and peer review

This article has undergone peer review.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.maturitas.2017.04.010.

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4.3 CAPÍTULO 3

Factors Associated with Sarcopenia and 7-Year Mortality in Very Old Patients with Hip Fracture Admitted to Rehabilitation Units: A Pragmatic Study

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Factors Associated with Sarcopenia and 7-Year Mortality in Very Old Patients with Hip Fracture Admitted to Rehabilitation Units: A Pragmatic Study

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Abstract: Background: Admitted bedridden older patients are at risk of the development of sarcopenia during hospital stay (incident sarcopenia). The objective of this study was to assess the factors associated with sarcopenia (incident and chronic) and its impact on mortality in older people with hip fracture. Methods: A multicenter, pragmatic, prospective observational study was designed. Older subjects with hip fracture admitted to two rehabilitation units were included. Sarcopenia was assessed at admission and at discharge according to the revised EWGSOP (European Working Group on Sarcopenia in Older People) consensus definition. The mortality was evaluated after 7 years of follow-up. Results: A total of 187 subjects (73.8% women) age 85.2 ± 6.3 years were included. Risk factors associated to incident and chronic sarcopenia were undernutrition (body mass index—BMI and Mini Nutritional Assessment–Short Form—MNA-SF), hand-grip strength and skeletal muscle index. During follow-up 114 patients died (60.5% sarcopenic vs. 39.5% non-sarcopenic, $p = 0.001$). Cox regression analyses showed that factors associated to increased risk of mortality were sarcopenia (HR: 1.67, 95% CI 1.11–2.51) and low hand-grip strength (HR: 1.76, 95% CI 1.08–2.88). Conclusions: Older patients with undernutrition have a higher risk of developing sarcopenia during hospital stay, and sarcopenic patients have almost two times more risk of mortality than non-sarcopenic patients during follow-up after hip fracture.

Keywords: skeletal muscle mass; sarcopenia; hip fracture; rehabilitation unit; mortality; very old patients; undernutrition

1. Introduction

Sarcopenia is a geriatric syndrome [1], characterized by the loss of muscle mass and function, which has been recognized as an independent clinical syndrome by the International Classification of

Disease, tenth revision, Clinical Modification (ICD-10CM) code (M62.84), thus strengthening its clinical significance [2,3]. In 2019 the European Working Group on Sarcopenia in Older People (EWGSOP) published the revised criteria for sarcopenia diagnosis, which included low hand-grip strength, low muscle mass and low gait speed [4].

Sarcopenia shares physio-pathological mechanisms, and is associated with a high prevalence of osteoporosis [5,6]. This situation has brought the introduction of the concept of osteosarcopenia, where sarcopenia and osteoporosis overlap resulting in important functional consequences like falls and hip fractures among others [7,8].

Hip fractures have an important impact upon the daily lives of people above 65 years, as over 40% of those who suffer a hip fracture do not recover the functional status they had prior to the fracture [9], and sarcopenia could be a factor influencing the loss of function [10]. In addition, hip fractures are associated with a high prevalence of institutionalization and mortality after 3 years (above 35%) [11]. Malnutrition is one of the physio-pathological mechanisms involved in the development of sarcopenia [12–14]. Oral supplementation has shown to be an important treatment for muscle mass preservation in older people with hip fracture [15,16].

The prevalence of sarcopenia in older people admitted to acute units with hip fractures varies between 17% and 37% [17,18], and increases in rehabilitation units up to 34% and 59% [19,20]. However, the percentage of very old subjects included in studies carried out in rehabilitation units usually is very low [19]. Therefore, the mean age of subjects included is not representative of older patients with hip fracture.

Sarcopenia is an important prognostic factor for mortality in older patients admitted to acute units [21–24]. Evidence regarding the effect of sarcopenia on the survival of older people with a hip fracture admitted to rehabilitation units is relatively limited.

Older people are often excluded from clinical trials [25], thus results of such trials have limited relevance to clinical practice [26]. In this sense, results of pragmatic studies enrolling real-life older people are very important to help in the daily clinical practice [27,28].

In this sense, the aim of this pragmatic study was to identify relevant factors associated to the presence of sarcopenia at admission and to the development of sarcopenia during a hospital stay in older patients admitted to post-acute wards for hip fracture rehabilitation, and to investigate the influence of sarcopenia on the risk of mortality after 7 years of follow-up.

2. Methods

2.1. Study Population

This pragmatic, prospective observational study included 187 subjects, older than 65 years of age admitted for rehabilitation after surgery due to hip fracture. The study was carried out at the post-acute rehabilitation units of two hospitals: Hospital San Juan de Dios in Pamplona (between January 2012 and August 2014), and Hospital Viamed Valvanera in Logroño (between November 2014 and December 2015), both located in Spain. The characteristics of these rehabilitation units have already been described [15]. Briefly, all those subjects suffering from a hip fracture are subjected to an orthopedic surgery. Patients with active medical processes who cannot return to their homes are referred to rehabilitation units, which are physically separate from hospitals for acute cases. Patients with pathological or periprotesic fractures, patients with fractures caused by traffic accidents, those with active oncologic pathologies and those receiving palliative care with a life expectancy of less than one year were not included in the study.

The protocol for this study was approved by the local ethics committee (Comité de Ética de Investigación Clínica de la Comunidad Foral de Navarra; Code number No. 33 of 17/2/2012). All subjects included signed informed consent forms. The protocol for this study was registered at the NIH ClinicalTrials.gov on November 22, 2011 (Identifier: NCT01477086). The study was carried out in accordance with the Helsinki Declaration.

2.2. Sarcopenia Assessment

Sarcopenia assessment was carried out upon admission, according to revised EWGSOP consensus definition [4]. Grip strength was measured with a digital dynamometer (DynX® Akern, Florence) following the standard protocol [29]. Grip strength was measured in both hands, and the better of two trials with each hand was recorded. Scores <27 kg in men or <16 kg in women were considered as low grip strength [4]. Muscle mass was assessed by bioimpedance analysis (BIA, Akern, Florence), resulting in scores for resistance (Rz) and reactance (Xc) expressed in ohms. The phase angle (PA) was also calculated, and expressed in degrees. The phase angle could be a representative marker of cell membrane integrity and vitality [30]. Low PA was considered for values <4.5 degrees [31]. Measurements were made in the morning, on fasting state, placing the electrodes (BIA Akern electrodes) on the ankle of the leg not subjected to surgery and on the wrist on the same side. Patients were placed in a supine position, on a non-conductive surface, arms separated from the upper body and legs slightly apart, so as to avoid contact between them. Appendicular skeletal muscle mass (ASMM) was calculated according to the formula [32]:

$$\text{ASMM} = -3.964 + (0.227 \times \text{RI}) + (0.095 \times \text{weight}) + (1.384 \times \text{sex}) + (0.064 \times \text{Xc}) \quad (1)$$

where RI is the resistive index calculated as (height in centimeters squared/Rz), weight in kg, and for the sex variable assuming values of 0 for women and 1 for men. Among the formulae validated for the assessment of muscle mass with BIA in older people, the formula put forward by Sergi et al. has demonstrated higher sensitivity and specificity [33]. The skeletal muscle mass index (SMI), corrected for height, was calculated with the following formula: SMI = ASMM/height in meters squared. SMI was defined as reduced for scores <7.0 kg/m^2 in men and <6.0 kg/m^2 in women [4].

Walking speed was measured with the 4 m walking test, considering scores ≤0.8 m/s as low gait speed. This measurement has been used as criterion for the sarcopenia severity assessment. Both measurements, muscle mass by BIA and hand-grip strength were carried out upon admission and 48 h before discharge. Walking speed was only measured upon discharge, due to patients' inability to walk steadily upon admission.

Sarcopenic patients have been defined as those with low hand-grip strength and low SMI considering the EWGSOP criteria recently published [4].

2.3. Patients Assessment

Demographic data (age, sex and marital status) were collected through an interview with the patient or a direct relative. Data concerning the type of fracture, time to surgery, type of surgery as well as post-surgery complications were collected throughout the medical history. The assessment of the nutritional status as well as anthropometric measurements (weight and height) and sarcopenia assessment (hand-grip strength, bio-impedance analysis and gait speed) were carried out by direct examination. Nutritional assessment was carried out by a nutritionist who used the Mini Nutritional Assessment-Short Form (MNA-SF) that classified patients as well nourished (12–14 points), at risk of malnutrition (8–11 points) and malnourished (0–7 points) [34]. Changes of weight, grip strength and SMI have been calculated as the difference between discharge and admission.

Functional capacity in the activities of daily living (ADL) was assessed by means of the Barthel index [35], which scores range from 0, totally dependent and 100, totally independent in the ADL. Information on previous BI scores from 15 days before the fracture was collected by an interview with patients or caregivers and upon discharge by direct examination (24 h before discharge). Cognitive capacities were assessed with the Spanish version of the Mini Mental State Examination (MMSE) [36]. MMSE was carried out during the first two weeks after admission to hospital.

Blood samples were analyzed in the first 72 h since admission and 48 h prior to discharge in order to determine hemoglobin, total proteins and albumin, Vitamin-D concentration and kidney function. In addition, inflammatory cytokines such as C-reactive protein (CRP), interleukin-6 (IL-6)

and tumor necrosis factor-alpha (TNF-alpha) were analyzed. For the study of insulin resistance the homeostasis model assessment (HOMA) index was calculated: HOMA = insulin (mcU/mL) × (glycemia (mmol/l)/22.5) [37].

2.4. Statistical Analysis

Patients were classified into four groups: Subjects with no sarcopenia neither admission nor discharge (control group); subjects with sarcopenia at admission and at discharge (chronic sarcopenia group); subjects with no sarcopenia at admission but develop sarcopenia during the hospital stay (incident sarcopenia group) and patients with sarcopenia at admission but revert this state during the hospital stay (reverted sarcopenia group). Variables are presented as the median and inter-quartile range (IQR) with the exception of categorized variables, which are presented as frequencies. Differences between the groups were assessed by the analysis of variance (ANOVA) for continuous data and by Pearson's χ^2 test for categorical data. The change of variables such as weight, SMI and hand-grip strength was calculated by the difference between values at discharge minus the values at admission. In order to investigate relevant factors associated with the risk of sarcopenia (chronic and incident) multiple logistic regression analyses were performed. Thus, the relationship between sarcopenia and clinical and functional variables was estimated by deriving odds ratios (ORs) from multiple logistic regression models. Sarcopenia (incident and chronic) was included as the dependent variable, and age, sex, length of hospital stay, functional ability (gait speed, hand-grip strength and Barthel index,), cognitive performance, nutritional assessment and body mass index (BMI) as independent factors.

In order to investigate the influence of sarcopenia (incident, chronic and the combination of the two types), as well as clinical and functional variables on the risk of mortality after 7-years of follow-up survival analyses were performed by means of Cox regression and Kaplan–Meier plots. The duration of the follow-up was calculated as the interval between the date of study entry (admission to the rehabilitation unit) and the date of death, loss to follow-up or the date the follow-up ended (31st of July of 2019), whichever came first. All the variables fitted the proportional hazard assumption. The Cox regression models were adjusted for potential confounders; sex, age and centre.

Values $p < 0.05$ were considered significant. Statistical analysis was done using SPSS and STATA.

3. Results

During the study period 206 patients with hip fracture were admitted of whom nine patients were excluded (five due to a serious clinical condition, two due to colon cancer and two due to having periprosthetic fractures). Of the 197 patients eligible for this study, 10 (5.1%) subjects died in the hospital. The final sample included a total of 187 subjects (73.8% women) with a mean age of 85.2 ± 6.3 years. Baseline characteristics are presented in Table 1. At admission sarcopenia was more prevalent in women (91.3%), without age differences between men and women (data not showed). Almost all patients lived at their own home before the fracture (99%), and only two (1%) patients lived in nursing homes.

During hospitalization some patients developed sarcopenia and others who had sarcopenia at admission reverted this state. Thus, four different groups of patients were considered in this study: (1) Those patients who were not sarcopenic at admission nor at discharge (controls, $n = 75$), (2) those that were not sarcopenic at admission but developed sarcopenia during their hospital stay (incident sarcopenia, $n = 54$), (3) those with sarcopenia at admission and at discharge (chronic sarcopenia, $n = 41$) and (4) those patients who were sarcopenic at admission, but reverted sarcopenia during the admission period (reverted sarcopenia, $n = 17$; Figure 1, flow chart of study population).

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Table 1. Baseline characteristics of the study sample.

	Total *n* = 187
Age, years	85.2 ± 6.3
Sex *n* (%)	
Female	138 (73.8%)
Male	49 (26.2%)
BMI kg/m^2	25.4 ± 4.6
Fracture type	
Intracapsular	89 (47.6%)
Extracapsular	98 (52.4%)
Type of surgery	
Replacement	69 (36.9%)
Internal fixation	118 (63.1%)
Time to surgery	2 (2–4)
Non-weight bearing	29 (15.5%)
LoS orthopedics (days)	10 (8–12)
LoS rehabilitation (days)	41 (29–57)
ONS [&]	73 (42.6%)
Previous Barthel index	85 (60–100)
MMSE	22 (16–26)
MNA-SF [‡]	10 (8–12)
SMI kg/m^2	
Female	13.6 ± 2.3
Male	17.2 ± 3.4
Grip strength kg	
Female	11.9 ± 5.0
Male	19.6 ± 9.6

MMSE: Mini Mental State Examination, LoS: length of stay, MNA-SF Mini Nutritional Assessment Short Form, ONS: oral nutritional supplementation. [&] ONS was available for 184 subjects. [‡] MNA-SF was available for 111 patients.

During admission 54 subjects developed sarcopenia, and 17 reverted sarcopenia. Differences between experimental groups were analyzed and are shown in Table 2. The chronic sarcopenia group was older than the other groups. No sarcopenic patients registered higher BMI than the rest of the subjects ($p < 0.0001$). Sex distribution differences were observed between groups ($p < 0.0001$). Men who were sarcopenic at admission reverted this state during the hospital stay. Among the 44 men who were non-sarcopenic at admission, 35 (79.5%) developed sarcopenia during the hospital stay. Regarding women, 53 (91.4%) were sarcopenic at admission and 12 of them reverted sarcopenia ($p < 0.0001$). Only 19 (35.2%) women developed sarcopenia during the hospital stay.

The chronic sarcopenia group registered lower PA value compared to controls (Table 2).

Variables included in the sarcopenia diagnosis criteria (SMI, hand-grip strength and gait speed) were statistically different among groups.

Men registered higher loss of skeletal muscle mass during the hospital stay without differences between experimental groups. On the other hand, women showed significant differences between groups on the change observed in skeletal muscle mass. Women in the incident sarcopenia group showed significantly higher muscle mass loss than the other groups, while those with reverted sarcopenia registered a slightly muscle mass increment reaching significant differences between groups (Table 2).

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Functional status as assessed by the Barthel index did not show relevant differences between experimental groups as well as the mini mental state examination. Interestingly, the mini nutritional assessment revealed significant differences between groups (Table 2).

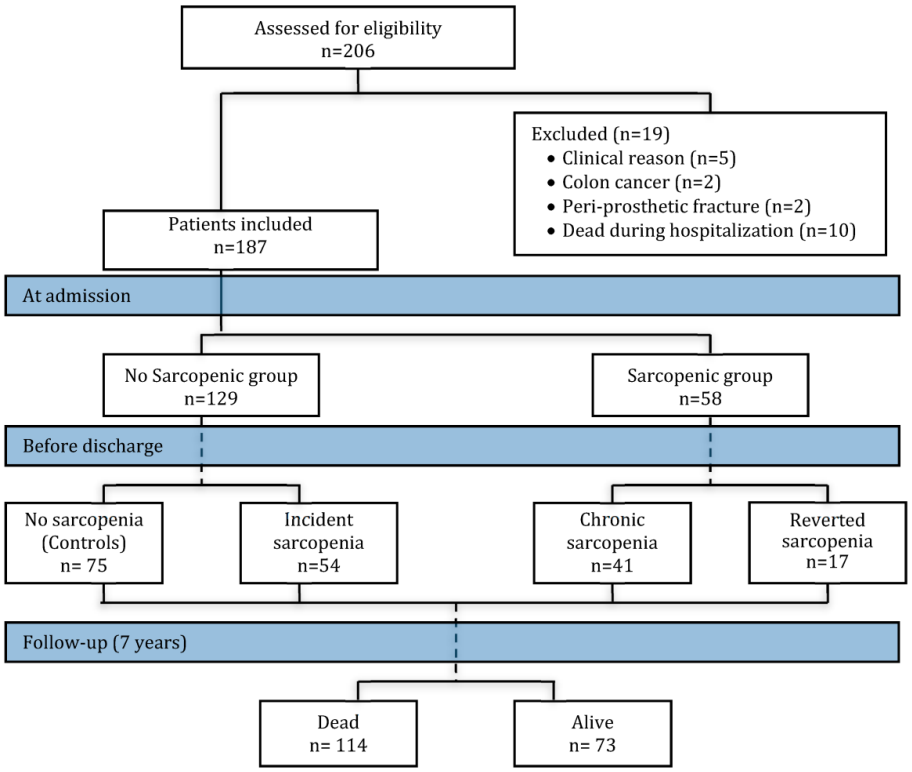

Figure 1. Flow chart of the study population and sarcopenia diagnosis at admission and at discharge. The assessment for sarcopenia was carried out at admission (the sample was divided as the no-sarcopenic and sarcopenic group) and before discharge (no-sarcopenic group at admission was divided as controls and incident sarcopenia, and the sarcopenic group at admission was divided as chronic sarcopenia and reverted sarcopenia). Total mortality was evaluated at 7 years of follow-up. Colored boxes indicate the time period (admission, discharge and follow-up period).

Table 2. Admission differences between patients considering different sarcopenic and non-sarcopenic groups.

	No Sarcopenic (Controls) *n* = 75	Incident Sarcopenia *n* = 54	Chronic Sarcopenia *n* = 41	Reverted Sarcopenia *n* = 17	*p*-Value
Age (year)	83.9 ± 5.6	86.1 ± 6.8	88.2 ± 4.6 ‡	81.1 ± 7.6	<0.0001
Sex *n* (M/W)	9/66	35/19	0/41	5/12	<0.0001
BMI, Kg/m^2	28.6 ± 4.7	23.9 ± 3.1 ‡	22.2 ± 2.8 ‡	23.6 ± 3.0 ‡	<0.0001
Weight, Kg	70.9 ± 15.0	62.1 ± 10.4 ‡ &	53.3 ± 7.4 ‡ #	59.0 ± 11.4 ‡	0.0001
SMI, Kg/m^2					
Men	7.4 ± 0.4 #-$	5.9 ± 0.6	NA *	6.4 ± 0.3	<0.0001
Women	6.1 ± 0.6 &-$	5.8 ± 0.7 &-$	4.9 ± 0.4	5.2 ± 0.3	<0.0001
Hand grip, kg					
Men	28.2 ± 11.3	15.6 ± 6.0 ‡ $	NA *	33.7 ± 3.3	<0.0001
Women	13.5 ± 5.9 &	12.3 ± 5.0	9.4 ± 3.0	12.4 ± 2.4	0.0008
Low hand-grip *n* (%)	42 (56%)	12 (22.2%)	41 (100%)	17 (100%)	<0.0001
Gait speed (m/s)	0.41 ± 0.22	0.36 ± 0.27	0.33 ± 0.22	0.54 ± 0.26 &	0.040
Previous BI	85 (69–100)	85 (55–100)	80 (60–97)	100 (85–100)	0.090
Discharge BI	60 (30–80)	50 (30–75)	55 (25–70)	75 (70–80)	0.069
MMSE	22 (16–27)	23 (16–27)	20 (15–25)	23 (17–26)	0.507
Phase Angle	4.5 ± 1.1 &	4.3 ± 1.4	3.7 ± 0.6	4.2 ± 1.1	0.010

Table 2. *Cont.*

	No Sarcopenic (Controls) $n = 75$	Incident Sarcopenia $n = 54$	Chronic Sarcopenia $n = 41$	Reverted Sarcopenia $n = 17$	p-Value
MNA-SF	11 (10–13)	12 (10–13)	10 (10–11) ‡	12 (10–12) &	0.005
Weight difference ¥, kg	−1.9 ± 3.4	−2.8 ± 3.4	−1.5 ± 2.6	−0.5 ± 3.0	0.054
SMI difference ¥, kg/m^2					
Men	−1.4 ± 2.0	−0.8 ± 1.7	NA *	−0.8 ± 1.7	0.872
Women	−0.6 ± 1.2 #-$	−1.8 ± 2.2 &-$	−0.2 ± 0.7 $	0.9 ± 1.2	<0.0001
Grip strength difference ¥, Kg					
Men	−1.2 ± 5.0	0.4 ± 3.8	NA *	0.5 ± 1.0	0.782
Women	0.96 ± 2.9	−0.33 ± 2.8 $	0.12 ± 2.3 $	3.5 ± 4.8	0.006

Results are expressed as mean ± SD, median (95% CI), or as n (%). NA: not available. ‡ differences vs. control group; # difference vs. incident group; & difference vs. chronic group and $ difference vs. reverted sarcopenia group. * results were not available because no men presented chronic sarcopenia. ¥ mean of the difference between values at discharge minus values at admission. BI: Barthel index, BMI: Body mass index, MMSE: Mini Mental State Examination, PA: Phase angle, SMI: Skeletal muscle index. MNA-SF: Mini nutritional assessment-short form.

Results from logistic regression analyses are shown in Table 3. Risk factors associated to both incident and chronic sarcopenia were low BMI, low hand-grip strength and low SMI.

Table 3. Logistic regression analysis considering incident or chronic sarcopenia as dependent variables and clinical indices as independent factors.

Variable	Incident *	p	Chronic ‡	p Value
BMI	0.73 (0.64–0.84)	<0.0001	0.64 (0.53–0.76)	<0.0001
MNA-SF	0.93 (0.65–1.33)	0.696	0.60 (0.40–0.90)	0.015
TST $	0.94 (0.88–1.01)	0.113	0.91 (0.85–0.98)	0.022
Hand-grip strength	0.92 (0.85–0.99)	0.038	0.85 (0.77–0.94)	0.002
SMI	0.17 (0.07–0.43)	<0.0001	0.002 (0.0002–0.03)	<0.0001
PA	0.97 (0.65–1.44)	0.896	0.41 (0.21–0.78)	0.007

Results are expressed as OR (95% CI); TST: Tricipital skinfold thickness. PA: Phase angle. $ TST was available for 49 patients. * Logistic regression analysis adjusted for age, sex and centre. ‡ Logistic regression analysis adjusted for age, and centre (not for sex because no male presented chronic sarcopenia).

In the logistic regression analysis performed considering chronic sarcopenia and reverted sarcopenia groups, main factors associated to sarcopenia reversion were the previous Barthel index (OR 0.95, 95% CI 0.90–0.99), hand-grip strength (OR 0.75, 95% CI 0.57–0.97) and SMI (OR 0.05, 95% CI 0.005–0.63), MNA-SF (OR 0.57, 95% CI 0.34–0.96) and CRP (OR 0.96, 95% CI 0.93–0.99).

3.1. Discharge Differences

At discharge 154 (82.4%) patients returned to their own homes, 19 (10.2%) were institutionalized in nursing homes and 14 patients (7.5%) were derived to another hospital due to complications or to complete the rehabilitation process.

Table 4 shows differences between sarcopenic patients (chronic and incident sarcopenic groups) and no sarcopenic patients (control and reverted sarcopenic groups). At discharge sarcopenia was more prevalent in men that in women (71% vs. 43%, $p = 0.001$). Patients with sarcopenia had lower BMI, higher TNF-alpha, lower hand-grip strength, SMI and gait speed.

Table 4. Discharge differences in sarcopenic and non-sarcopenic patients.

	Sarcopenia *n* = 95	No Sarcopenia *n* = 92	*p*-Value
Sex *n* (M/W)	35/60	14/78	0.001
Weight, Kg	56.1 ± 9.4	66.4 ± 13.9	<0.001
BMI, Kg/m^2	22.3 ± 2.8	26.9 ± 4.5	<0.001
Hb, g/dL	11.9 ± 1.2	11.6 ± 1.0	0.046
Total Protein, g/dL	6.2 ± 0.6	6.2 ± 0.5	0.616
Albumin, g/dL	3.5 ± 0.4	3.5 ± 0.4	0.921
VitD ng/mL	11 (12.7–24.9)	16 (12–23.5)	0.481
IL-6, pg/mL	6.2 (3.6–9.3)	6.0 (3.9–8.4)	0.753
TNF-alpha, pg/mL	11.3 (8.0–15.8)	7.5 (5.0–12.4)	0.022
Barthel index	50 (30–75)	65 (35–80)	0.053
MNA-SF	11.5 (10–12.7)	11.5 (10.5–12.5)	0.880
PA	3.9 ± 0.7	4.4 ± 0.8	0.0001
Hand-grip, kg	12.8 ± 5.4	16.7 ± 7.9	0.001
Men	17.2 ± 5.6	32.3 ± 4.2	<0.001
Women	10.2 ± 3.3	14.8 ± 5.8	<0.001
Low grip strength *n* (%)	95 (100%)	43 (46.7%)	<0.0001
SMI, Kg/m^2			
Men	5.7 ± 0.6	6.9 ± 0.7	<0.001
Women	5.0 ± 0.4	5.9 ± 0.6	<0.001
Low SMI *n* (%)	95 (100%)	20 (21.7%)	<0.0001
Gait speed, m/s	0.3 ± 0.2	0.4 ± 0.2	0.035
Low gait speed *n* (%)	80 (84.2%)	68 (73.9%)	0.083

BMI: Body mass index, Hb: Hemoglobin, IL-6: Interleukin-6, SMI: Skeletal muscle index, TNF-alpha: Tumor necrosis factor-α, VitD: Vitamin D.

3.2. Mortality

After a mean follow-up period of 3.9 ± 2.1 years, 114 (61%) patients died (71.9% women vs. 28.1% men, $p = 0.468$) 60.5% were sarcopenic vs. 39.5% non-sarcopenic ($p = 0.001$). Mortality was more frequent among sarcopenic than non-sarcopenic patients (72.6% vs. 48.9%, $p = 0.001$). Deceased were older than alive patients (86.6 ± 6.0 vs. 83.0 ± 6.1 years; $p = 0.0001$).

Cox regression analyses as well as Kaplan–Meier plots showed that sarcopenia was associated with the risk of total mortality (Figure 2, panel A). On the other hand, low hand-grip also presented a significant association with mortality (Figure 2 panel B), while SMI and gait speed showed a non-significant association with the risk of mortality (Figure 2 panel C and D).

When different sarcopenic groups were considered, chronic and incident sarcopenia showed a similar association with the risk of mortality HR: 1.60 (0.93–2.76; $p = 0.087$) and HR: 1.59 (0.97–2.63; $p = 0.065$), respectively, without reaching statistical significance, while the reverted sarcopenia group was not associated to the risk of mortality HR: 0.98 (0.45–2.12; $p = 0.960$).

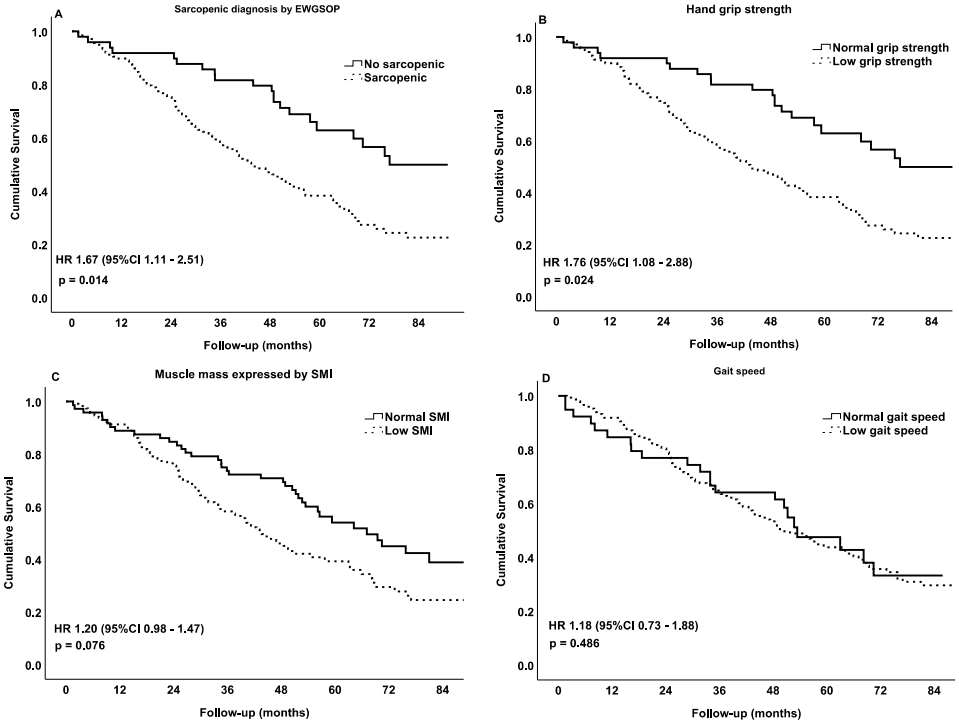

Figure 2. Cox regression of cumulative survival at 7 years of follow-up expressed with the Kaplan–Meier curve (n = 187). Variables included at discharge. Models adjusted by age, sex and centre. (**A**) Sarcopenia diagnosis by the revised European Working Group on Sarcopenia in Older People; (**B**) low hand-grip strength <27 kg for men, and <16 kg for women; (**C**) low skeletal muscle index <7.0 kg/m^2 for men, and <6.0 kg/m^2 for women and (**D**) low gait speed ≤0.8 m/s.

4. Discussion

The present research aimed to identify factors involved in the incidence of sarcopenia, and also to assess the association of sarcopenia with the risk of mortality during a follow-up period of 7 years in older patients with hip fracture.

Our results show that almost 42% of patients developed sarcopenia during hospitalization. As it could be expected, higher muscle mass and hand-grip strength, but also a correct nutritional status, are important protective factors against the incidence of sarcopenia. Many factors favor muscular atrophy, such as age [38], bedrest and a sedentary lifestyle [39]. It is known that the loss of muscle mass is associated with the reduction of strength [40]. However, in line with previous observations [22,41], a significant association between nutritional status and the incidence of sarcopenia was observed in the present study, being patients with higher BMI and MNA-SF those with lower risk for developing sarcopenia. The BMI of the subjects included in this study was within the range defined as normal, but we observed that higher values of BMI (slight overweight) protected against incident sarcopenia. In this sense, it is very important to pay attention to the nutritional status of the elderly with hip fractures and a normal BMI [42,43] since these subjects should be beneficiaries of nutritional supplements, as recommended in the last ESPEN guidelines [44,45]. On the other hand, the relatively high BMI observed in non-sarcopenic subjects could also suggest that being slightly overweight might be a protective factor against adverse events and mortality in older people [16].

Undernutrition is an important mechanism that can promote the onset of sarcopenia [12,46,47], and could explain the increase in the prevalence and incidence of sarcopenia among subjects with no reduced BMI [48]. Insufficient intake contributes to the loss of muscle mass and strength [49], and nutritional supplementation could effectively treat sarcopenia [16,50]. In a previous publication by our

group it was described how nutritional supplementation prevents the loss of muscle mass during the functional rehabilitation process after a hip fracture [15].

Considering our results it is interesting to note that 29% of patients reverted sarcopenia during hospitalization being the previous Barthel index, nutritional status, strength and muscle mass the main factors associated to this process.

Sarcopenia [51], as well as frailty [52], are two important reversible geriatric syndromes, and nutritional status has shown to play a very important role on evolution and mortality risk of older adults with hip fracture [16,53,54]. Nutritional intervention [55–57], as well as physical exercise [58,59], have been described as effective therapies in the prevention and treatment of sarcopenia.

In the present study only 10% of males were sarcopenic at admission, and the 65% of those who developed sarcopenia during hospitalization were males. In agreement with previous studies [19,60,61], the prevalence of sarcopenia at discharge was greater in males (71%) than in females (43%).

Various possible mechanisms have been proposed to explain the pathophysiological differences of sarcopenia between males and females [62,63]. It will be interesting in the future to analyze in more detail the muscle metabolism of older people after a hip fracture.

In this study we found very high mortality (61%) considering the large follow-up, showing that sarcopenia, defined with the revised EWGSOP criteria, was significantly associated with 1.7 times more risk of death. Other research studies have shown the association between sarcopenia, defined by the EWGSOP, and the increased risk of mortality in older patients admitted to a geriatric acute wards [64].

On the other hand, and as it was expected, hand-grip strength was associated with a higher probability of death with 1.8 times more mortality risk in patients with reduced hand grip strength in comparison to those with normal hand grip strength. Accordingly, previous studies had shown an increase in mortality associated with both low grip strength [65] and loss of hand-grip strength [66] in older community dwelling subjects.

We did not find any studies that evaluated the association of sarcopenia, defined with the revised EWGSOP criteria, and mortality in elderly with hip fractures hospitalized in rehabilitation units.

Regarding gait speed, no significant associations were observed between gait speed and mortality. This result could be explained due to the fact that almost the totality of the sample showed a low gait speed.

Prior studies have demonstrated that the ability to walk is relatively swiftly recovered following a hip fracture [67], but the recovery of the ability to walk (gait-speed) that patients had before the fracture is usually slow and partial [68], sometimes the recovery is only partial and associated with the onset of a physical disability [69]. In 2011 Studensky et al. already observed the reduced impact of gait speed on survival in very old patients [70].

This study has a number of limitations. Firstly, characteristics of patients not admitted to the rehabilitation units were not available. It is possible that these patients made more rapid progress, and they probably had less sarcopenia, so that the actual prevalence of sarcopenia could be lower in older patients with a hip fracture. Secondly, the measurement of muscle mass was carried out indirectly by BIA, which it is known to present some drawbacks associated with the state of hydration. Nevertheless, we tried to make a measurement of the BIA in the same conditions in all patients. It must be taken into account that BIA is very cheap, easy to use and quickly reproducible, being the better method to assess body composition in ambulatory and bedridden patients. Third, we do not know the cause of death, not knowing whether it was associated directly with sarcopenia or with its possible complications, or if it was secondary to other causes. Finally, taking into account the observational design of the study we cannot discard other possible confounding factors that are not being considered. Nevertheless the sample was very homogeneous and the prospective design of the study allowed us to evaluate the evolution of patients during hospitalization.

Despite these possible limitations, this study has several strengths. The average age of the participants is quite high, so it could be considered as representative of the geriatric population. There are not many studies of sarcopenia, defined according to recently revised EWGSOP criteria, with a

very old population and such a large follow-up. Probably the main strength of this study was its pragmatic design [28], which allowed us to hypothesize that the results could be extrapolated to the rest of geriatric patients admitted to rehabilitation units.

5. Conclusions and Implications

Sarcopenia is very prevalent in older people with fractures admitted to rehabilitation units and is associated with long-term mortality. Fall prevention and early treatment of sarcopenia (with correction of nutritional deficits and physical exercise) should be two important healthcare policies in the ageing population. Sarcopenia is considered a reversible geriatric syndrome, so future research should assess whether the reversion of sarcopenia is associated with a decrease in mortality. Sarcopenia is associated with malnutrition, which at the same time is associated with adverse events in older people with a hip fracture, so that, an in-depth nutritional assessment to assure the proper treatment may be effective in the prevention or reversion of sarcopenia, improving the recovery of very old patients with a hip fracture.

Author Contributions: Study concept and design: V.M. Acquisition of data: V.M. Analysis and interpretation of data: V.M., I.A.G., M.A.Z. Drafting of the manuscript: V.M., C.M., A.B.U., J.A.M., I.A.G., M.A.Z. Critical revision of the manuscript for important intellectual content: V.M., C.M., A.B.U., J.A.M., I.A.G., M.A.Z. V.M. was the principal investigator. This research is part of V.M.'s Ph.D. project. M.A.Z. was the supervisor of the Ph.D. project, and contributed to the critical analysis of findings and the writing and editing of this paper.

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5 DISCUSIÓN

Las personas mayores con fractura de cadera presentan una ingesta inadecuada a sus requerimientos, y esto causa un empeoramiento de su ya comprometido estado nutricional. Utilizando el MNA como herramienta de cribado se objetiva que la prevalencia de malnutrición es de alrededor del 19%, pero esta puede aumentar hasta casi el 46% si se utilizan otros marcadores para el diagnóstico de malnutrición, como el índice de masa corporal, la pérdida de peso o la concentración de albúmina.

Si bien no exista una medida estándar para definir el estado nutricional deseable, se han desarrollado numerosos instrumentos de detección y evaluación en un esfuerzo por capturar los factores de riesgo establecidos y los signos y síntomas clínicos de la desnutrición (Green y Watson, 2006).

Es ampliamente reconocido que la definición estándar de la Organización Mundial de la Salud (OMS) de IMC normal para minimizar la morbilidad y la mortalidad no es aplicable para las poblaciones geriátricas.

Hasta la fecha, no se han realizado ajustes de edad a la recomendación de la OMS de 18,5–24,9 kg/m^2, y hasta hace poco existía un desacuerdo con respecto a la validez de su uso para predecir la mortalidad (Ben-Yacov et al., 2017). Esta controversia, conocida como "la paradoja del IMC", fue ampliamente publicitada y presentó evidencia que indica que las personas clasificadas como con sobrepeso (25-29,9 kg/m^2) en realidad pueden beneficiarse de tasas de mortalidad más bajas (Flegal et al., 2013). Posteriormente, se argumentó que la paradoja del IMC se basa en errores metodológicos y estadísticos .

El rango de IMC óptimo recomendado de 23 a 29 kg/m^2 para la mortalidad más baja por todas las causas para los ancianos sería más preciso que el rango de IMC recomendado actualmente de 20 a 25 kg/m^2 para todos los adultos (Aune et al., 2016; Global y Mortality, 2016), y ciertamente más precisa que la recomendación de la OMS de 18,5–25 kg/m^2. Como el rango deseable de IMC de 23 a 29 kg/m^2 se superpone al rango de 25 a 30 kg/m2, considerado sobrepeso, parece que la paradoja del IMC es válida para las personas mayores, lo que demuestra que un poco de peso adicional es beneficioso.

La pérdida media de altura acumulada entre los 30 y 70 años es de aproximadamente 3 cm para los varones y 5 cm para las mujeres; a la edad de

80 años, puede aumentar hasta 5 cm para los varones y 8 cm para las mujeres. Este grado de pérdida de altura explicaría un aumento "artificial" en el IMC de aproximadamente 0,7 kg/m^2 para los varones y 1,6 kg/m^2 para las mujeres a la edad de 70 años que aumenta hasta 1,4 y 2,6 kg/m^2, respectivamente, por encima de los 80 años de edad (Sorkin et al., 1999).

Estas preocupaciones pueden amplificarse en mujeres mayores, dado que ocurren cambios importantes relacionados con la composición corporal después de la menopausia, como una disminución en la densidad mineral ósea y la masa muscular, y el aumento y la redistribución de la masa grasa (con un aumento de la adiposidad central) (Toth et al., 2000), que puede estar enmascarado por un IMC normal que resulta en el fenotipo llamado obesidad sarcopénica.

Un IMC bajo (<22 kg/m^2) se asocia con un aumento del riesgo de fractura de un 38% y de la mortalidad por todas las causas de un 52% (Miller et al., 2009)

La malnutrición, definida como la presencia de índices antropométricos reducidos se asocia con mayor prevalencia de complicaciones durante la hospitalización y con peor recuperación funcional (Daniel D. Bohl et al., 2017; Inoue et al., 2017; Mazzola et al., 2017; Papadimitriou et al., 2017). A pesar de la mejora en la asistencia de los pacientes con fractura de cadera, la mortalidad sigue siendo demasiado elevada (se calcula una mortalidad de alrededor del 30% a un año tras la fractura, y de hasta el 40% a 3 años), y la desnutrición parece influir de forma negativa aumentando el riesgo de mortalidad (Menéndez-Colino et al., 2018; van Wissen et al., 2016; Vosoughi et al., 2017).

El segundo objetivo de este trabajo de investigación era valorar los beneficios de la suplementación nutricional oral enriquecida con HMB y vitD durante la recuperación funcional en pacientes mayores con fractura de cadera. Los resultados observados demuestran que los sujetos que reciben suplemento nutricional oral tienen menos complicaciones, menor sarcopenia (mejora la masa muscular apendicular al alta) y presentan mejor situación nutricional al alta (no pierden peso, como se observa en el grupo control), además del restablecimiento de valores normales de proteínas plasmáticas totales. D'Adamo y colaboradores (2014) demostraron que en los 60 días sucesivos a la fractura de cadera se observa una significativa pérdida de masa muscular, (D'Adamo et al., 2014) pérdida evidente también en la cirugía de

cadera de elección (Kouw et al., 2018). Este estudio ha encontrado el mismo resultado en el grupo control, mientras que los sujetos que han recibido suplemento nutricional oral durante la recuperación funcional han mejorado su masa muscular apendicular al alta. En este estudio la prevalencia de sarcopenia (72%) es mayor que la observada en estudios realizados en la comunidad (4-25%) (Hirani et al., 2015; Landi et al., 2012b), en hospitales (25%) (Rossi et al., 2014; Smoliner et al., 2014) o en residencia (32%) (Landi et al., 2012a; Senior et al., 2015). Varios aspectos pueden haber influido sobre este resultado. El primero es que el alto grado de heterogeneidad en la definición y en la medición de la sarcopenia hace que los resultados de los diferentes estudios sean difícilmente comparables (Malafarina et al., 2012). Por otra parte la edad media de los pacientes (casi 86 años) es más alta que la de estudios anteriores (Rossi et al., 2014). Tercero, este estudio se realizó en unidades de rehabilitación en las que ingresan los pacientes clínicamente más complicados, respecto a los pacientes dados de alta de unidades de ortogeriatría (Vidán et al., 2005). En último lugar, en los ancianos con fractura de cadera la recuperación de la marcha, uno de los parámetros diagnósticos de sarcopenia, es más lenta que la recuperación de otros aspectos de la capacidad funcional (como vestirse, continencia o comer) (Ortiz-Alonso et al., 2012).

A pesar de la elevada prevalencia de sarcopenia, el 68% de los sujetos del grupo de intervención recuperan su propio estado funcional previo a la fractura, más que en estudios anteriores sin suplementos nutricionales (Uriz-Otano et al., 2016). La suplementación nutricional oral se asocia a menor número de complicaciones, a estancias medias más cortas en unidades de ortogeriatría (Anbar et al., 2014; Espaulella et al., 2000), y se asocia además a menor pérdida de peso (Myint et al., 2013). Las principales causas de los limitados beneficios observados con la suplementación nutricional oral en estudios anteriores podría estar relacionado con la elección de sujetos que realmente no presentaban malnutrición y por lo tanto no precisan suplementación nutricional, con el tipo de suplemento utilizado y la duración del mismo (Avenell y Handoll, 2010; Malafarina et al., 2013c), observando una gran heterogeneidad en cuanto a los suplementos indicados, duración de los estudios, cumplimiento terapéutico y medición de la masa muscular.

Los bajos niveles de vitD se asocian con una reducción de la masa y de la fuerza muscular (Visvanathan y Chapman, 2010), y con síntomas como el dolor muscular (Beaudart et al., 2014), siendo la suplementación eficaz en la prevención y en el tratamiento de la fragilidad (Artaza-Artabe et al., 2016). En esta investigación se ha observado que la cantidad de VitD contenida en el suplemento nutricional utilizado ha sido eficaz en restablecer valores normales de vitamina D en la casi totalidad de los pacientes tratados.

En relación al perfil glucémico se observó un ligero aumento de la concentración de insulina y de los valores del índice HOMA en el grupo de intervención, pudiendo explicar esta evidencia como un resultado positivo desde el punto de vista metabólico. La leucina, y el HMB, estimulan la secreción de insulina, pudiendo considerar el aumento de la concentración de insulina observado en el grupo de intervención como una evidencia del cumplimiento del tratamiento nutricional. El HMB es uno de los estimulantes más potentes de mTOR (*mamalian target of rapamycin kinasa*), que es la llave reguladora del crecimiento celular muscular (D'Antona y Nisoli, 2010). En presencia de cantidades suficientes de aminoácidos y de HMB, la insulina activa una cascada seguida de la estimulación de mTOR, que determina un aumento de la síntesis proteica muscular (Cleasby et al., 2016). Todo este mecanismo podría ser la base de los resultados obtenidos. La citoquina proinflamatoria IL-6 es también conocida como una miokina, ya que es producida por las células musculares, en respuesta al ejercicio físico regular, en ausencia de daño muscular (Raschke y Eckel, 2013). A pesar de la marcada reducción en ambos grupos de la concentración de IL-6 respecto al ingreso, la persistencia de valores relativamente altos podría estar en relación con la realización de la rehabilitación, y ser considerado por lo tanto, un marcador positivo de activación muscular (Fischer, 2006).

El tercer objetivo de la presente investigación era identificar los factores de riesgo para el desarrollo de sarcopenia y también evaluar la asociación de la sarcopenia con el riesgo de mortalidad durante un período de seguimiento de 7 años en pacientes mayores con fractura de cadera.

Los resultados obtenidos muestran que casi el 42% de los pacientes desarrollaron sarcopenia durante la hospitalización. Como era de esperar, tanto la mayor masa muscular y la fuerza de prensión de la mano, así cómo también

un IMC más alto son importantes factores protectores contra la incidencia de sarcopenia. Muchos factores favorecen la atrofia muscular, como la edad (Short et al., 2005), el reposo en cama y un estilo de vida sedentario (Martone et al., 2017). La pérdida de masa muscular se asocia con la reducción de la fuerza (Masanes et al., 2012). Sin embargo, en línea con observaciones anteriores (Cerri et al., 2015; Landi et al., 2013), en esta investigación se observó que los pacientes con IMC y MNA-SF más altos presentan menor riesgo de desarrollar sarcopenia.

El IMC de los sujetos incluidos en este estudio estaba dentro del rango definido como normal, pero observamos que los valores más altos de IMC (sobrepeso leve) protegían contra la sarcopenia incidente. En este sentido, es muy importante prestar atención al estado nutricional de los ancianos con fracturas de cadera e IMC normal (Gómez-Cabello et al., 2013; Parr et al., 2013) ya que estos sujetos podrían beneficiarse de suplementos nutricionales, como se recomienda en las últimas guías ESPEN (Volkert et al., 2019). Por otro lado, el IMC relativamente alto observado en sujetos no sarcopénicos también podría sugerir que tener un ligero sobrepeso podría ser un factor protector contra los eventos adversos y la mortalidad en las personas mayores (Malafarina et al., 2018).

La desnutrición es un mecanismo importante que puede promover la aparición de sarcopenia (Bibiloni et al., 2018; Robinson et al., 2018; Sánchez-Rodríguez et al., 2019), y podría explicar el aumento en la prevalencia e incidencia de sarcopenia entre los sujetos a pesar de tener un IMC normal (Landi et al., 2018). La ingesta insuficiente contribuye a la pérdida de masa y fuerza muscular (Malafarina et al., 2013a), y la suplementación nutricional podría tratar eficazmente la sarcopenia (Malafarina et al., 2018, 2013c).

Teniendo en cuenta nuestros resultados, es interesante observar que el 29% de los pacientes revirtieron la sarcopenia durante la hospitalización, siendo el índice de Barthel anterior, el estado nutricional, la fuerza y la masa muscular fueron los principales factores asociados a este proceso.

La sarcopenia (Cruz-Jentoft y Sayer, 2019), así como la fragilidad (Lorenzo-López et al., 2019), son dos síndromes geriátricos reversibles importantes, y el estado nutricional ha demostrado desempeñar un papel muy importante en la evolución y en el riesgo de mortalidad de los adultos mayores con fractura de

cadera (Clegg y Williams, 2018; Granic et al., 2018; Malafarina et al., 2018). La intervención nutricional (Aquilani et al., 2017; Sanz-Paris et al., 2018; Trouwborst et al., 2018), así como el ejercicio físico (Martínez-Amat et al., 2018), se han descrito como terapias efectivas en la prevención y en el tratamiento de la sarcopenia.

En el presente estudio, solo el 10% de los hombres eran sarcopénicos al ingreso, sin embargo, el 65% de los que desarrollaron sarcopenia durante la hospitalización eran hombres. De acuerdo con estudios previos [19,61,62], la prevalencia de sarcopenia al alta fue mayor en hombres (71%) que en mujeres (43%).

Se han propuesto varios mecanismos posibles para explicar las diferencias fisiopatológicas de la sarcopenia entre hombres y mujeres (Renoud et al., 2014; Tay et al., 2015). Será interesante en el futuro analizar con más detalle el metabolismo muscular de las personas mayores después de una fractura de cadera.

En este estudio, encontramos una mortalidad muy alta (61%) considerando el gran seguimiento, que muestra que la sarcopenia, definida con los criterios revisados EWGSOP, se asoció significativamente con un riesgo de muerte 1,7 veces mayor. Otros estudios de investigación han demostrado la asociación entre la sarcopenia, definida por el EWGSOP, y el mayor riesgo de mortalidad en pacientes mayores ingresados en salas geriátricas agudas (Sipers et al., 2019).

Por otro lado, y como era de esperar, la fuerza de prensión manual se asoció con una mayor probabilidad de muerte con un riesgo de mortalidad 1.8 veces mayor en pacientes con una fuerza de prensión reducida en comparación con aquellos con fuerza de prensión normal. En consecuencia, estudios previos habían mostrado un aumento en la mortalidad asociada con una baja fuerza de prensión (Granic et al., 2017) y una pérdida de la fuerza de agarre de la mano (Syddall et al., 2017) en sujetos de vivienda comunitaria de mayor edad.

No encontramos ningún estudio que evaluara la asociación de la sarcopenia, definida con los criterios revisados de EWGSOP, y la mortalidad en ancianos con fracturas de cadera hospitalizados en unidades de rehabilitación.

En cuanto a la velocidad de la marcha, no se observaron asociaciones significativas entre la velocidad de la marcha y la mortalidad. Este resultado

podría explicarse debido al hecho de que casi la totalidad de la muestra mostró una baja velocidad de marcha.

Estudios previos han demostrado que la capacidad de caminar se recupera relativamente rápido después de una fractura de cadera (Ortiz-Alonso et al., 2012), pero la recuperación de la capacidad de caminar (velocidad de la marcha) que tenían los pacientes antes de la fractura suele ser lenta y parcial (Karlsson et al., 2016), a veces la recuperación es solo parcial y está asociada con el inicio de una discapacidad física (Uemura et al., 2018). En 2011 Studensky y colaboradores observaron el reducido impacto de la velocidad de la marcha en la supervivencia en pacientes de edad muy avanzada (Studenski et al., 2011).

5.1 Limitaciones y puntos de fuerza

Este estudio presenta algunas limitaciones. Primero no se ha vuelto a medir la masa muscular, la fuerza de prensión de la mano ni la velocidad de la marcha tras el alta. Segundo, no disponemos de las características de los pacientes dados de alta directamente de la unidad de traumatología. En estos últimos pacientes la recuperación podría ser más rápida, y probablemente tendrían menos sarcopenia, por lo que la prevalencia de sarcopenia podría ser menor en pacientes ancianos con fractura de cadera. Por otro lado este estudio tiene fortalezas que conviene resaltar. Primero que la edad media de los sujetos incluidos es muy avanzada, representativa de la población geriátrica. En este sentido no existen prácticamente estudios a nivel científico con sujetos de edad tan avanzada. Además el estudio ha sido realizado en dos hospitales de rehabilitación, con pacientes de la vida real, observando que las características de los pacientes derivados a las unidades de rehabilitación son parecidas.

6 CONCLUSIONES

1. La prevalencia de desnutrición es muy alta en las personas mayores, aumentando en pacientes geriátricos con alta comorbilidad. La malnutrición se asocia con alteraciones funcionales, siendo tanto causa como consecuencia de las fracturas de cadera. La prevención de la malnutrición podría contribuir a reducir la incidencia de fracturas, y mejorar la recuperación funcional tras una fractura de cadera. La inclusión de la valoración y tratamiento nutricional en los planes de asistencia en pacientes geriátricos pueden favorecer una mejor recuperación funcional y una reducción de la mortalidad.

2. En los pacientes mayores con fractura de cadera, la suplementación oral con HMB mejora la masa muscular (sarcopenia), previene la pérdida de peso y por lo tanto el desarrollo de malnutrición, y ayuda en la recuperación funcional. Los suplementos nutricionales orales con HMB pueden ser un tratamiento eficaz para reducir la sarcopenia y la malnutrición y pueden prevenir el desarrollo de discapacidad secundaria a la fractura de cadera en pacientes mayores.

3. Los pacientes mayores con desnutrición mostraron mayor riesgo de desarrollar sarcopenia durante la estancia hospitalaria. Además los pacientes sarcopénicos presentaron dos veces mayor riesgo de mortalidad que los pacientes no sarcopénicos durante el seguimiento tras una fractura de cadera.

4. Conclusión global: la literatura científica pone de manifiesto la alta prevalencia de malnutrición en personas mayores con fractura de cadera. Las fracturas de cadera siguen siendo una causa importante de discapacidad, institucionalización y mortalidad prematura. El músculo es un importante marcador del estado nutricional reconociendo la mala salud muscular como el principal factor asociado a las caídas. La suplementación nutricional oral mejora el estado nutricional así como la sarcopenia en las personas mayores con fractura de cadera.

   Por todo ello podemos concluir que, la prevención de la malnutrición y una intervención nutricional temprana conllevan una mayor recuperación

funcional tras una fractura de cadera. Investigaciones futuras se deberían centrar en valorar si la reversión de la sarcopenia garantiza una vida libre de discapacidad física así como una reducción de la mortalidad en este tipo de pacientes.

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