FACULTAD DE MEDICINA
Departamento de Medicina Preventiva,
Salud Pública y Microbiología

LA ESTANDARIZACION DEL FENOTIPO DE FRAGILIDAD.
EL ESTUDIO DE ENVEJECIMIENTO SALUDABLE DE TOLEDO.

TESIS DOCTORAL

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DIRECTORES

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Madrid, 2017

INFORME DEL DIRECTOR DE TESIS PARA LA AUTORIZACIÓN DE DEFENSA DE TESIS DOCTORAL

D. LEOCADIO RODRIGUEZ MAÑAS

Director de la tesis doctoral de Dª CRISTINA ALONSO BOUZÓN

informa favorablemente la solicitud de autorización de defensa de la tesis doctoral con el Título **LA ESTANDARIZACIÓN DEL FENOTIPO DE FRAGILIDAD. EL ESTUDIO DE ENVEJECIMIENTO SALUDABLE DE TOLEDO.**

presentada por dicha doctoranda.

Programa de Doctorado: RD1393/2007
La tesis está sometida a procesos de confidencialidad: SÍ ☐ NO X
La tesis se presenta como compendio de publicaciones: SÍ ☐ NO X

Resultados y valoración:

ANTECEDENTES DE LA CUESTIÓN Y OBJETIVOS PROPUESTOS

Si bien la fragilidad es el punto clave en la prevención de la discapacidad y en la promoción del envejecimiento saludable, no existe una definición conceptual ni operativa que haya logrado el salto definitivo a la práctica clínica. Entender los mecanismos fisiopatológicos que subyacen el desarrollo de la fragilidad, identificando nuevos procesos implicados, podría ayudar a avanzar en la comprensión de este concepto en aras de desarrollar un mejor instrumento que permita detectar la fragilidad en la práctica clínica diaria. Objetivos:

1-. Hacer una revisión bibliográfica de los mecanismos fisiopatológicos conocidos que subyacen el desarrollo de fragilidad, así como de las intervenciones farmacológicas evaluadas hasta el momento para el manejo clínico de la fragilidad.

2-. Evaluar la relación entre disfunción endotelial, medida por niveles de DiMetilArginina Asimétrica –ADMA-, y fragilidad.

3-. Comparar la prevalencia de modificaciones en la categorización funcional de los sujetos (robusto/prefrágil/frágil) de la cohorte del Estudio Toledo de Envejecimiento Saludable (ETESsegún se utilicen los Criterios del Fenotipo de Fragilidad (CFF) con los puntos de corte originales de Linda P. Fried o los CFF con los puntos de corte estandarizados a la población española (S-CFF). Comparar si la modificación en las categorías diagnósticas supone también una modificación de los riesgos de hospitalización, muerte, discapacidad incidente y caídas.

4-. Construir árboles de decisión para los outcomes de muerte y desarrollo de nuevas discapacidades (o discapacidad incidente) a cinco años.

DESARROLLO DEL TRABAJO Y METODOLOGÍA

El trabajo se divide en cuatro objetivos:

1- Para alcanzar el primero de ellos se realizó una revisión bibliográfica.
2- Para resolver los otros tres objetivos, se realizaron análisis estadísticos con los datos del estudio de Envejecimiento Saludable de Toledo (cohorte diseñada con el objetivo de estudiar el envejecimiento y la fragilidad en población española).

APORTACIONES DE CARÁCTER GENÉRICO O EXPERIMENTAL

La tesis aporta resultados de carácter genérico, extrapolables a toda la población anciana.

PUBLICACIONES A QUE HAYA DADO LUGAR

1-. Laosa O, Alonso Bouzon C, Castro M, Rodriguez Mañas L. Pharmaceutical interventions for frailty and sarcopenia. Current Pharmaceutical design. 2014;20(18):3068-82. PMID 24079768 Factor de Impacto 2015: 3.052.

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3-. Alonso Bouzón C, Carnicero JA, Gonzáles Turín J, García-García FJ, Esteban de la Torre A, Rodríguez-Mañas L. The standarization of frailty phenotype criteria improves its predictive ability. The Toledo study for healthy aging. JAMDA 2017, 2. pii: S1525-8610(16)30520-5. doi: 10.1016/j.jamda.2016.11.003. (Epub ahead of print). Factor de Impacto 2015: 6.616

VALORACIÓN GLOBAL

Los resultados de esta tesis apoyan la necesidad de introducir cambios en la práctica clínica en el manejo del paciente anciano.

Se autoriza la presentación de la tesis como compendio de publicaciones: SÍ ☐ NO X

Fecha

Firma

INFORME DEL DIRECTOR DE TESIS PARA LA AUTORIZACIÓN DE DEFENSA DE TESIS DOCTORAL

D. ANDRÉS ESTEBAN LATORRE

Director de la tesis doctoral de Dª CRISTINA ALONSO BOUZÓN

informa favorablemente la solicitud de autorización de defensa de la tesis doctoral con el Título **LA ESTANDARIZACIÓN DEL FENOTIPO DE FRAGILIDAD. EL ESTUDIO DE ENVEJECIMIENTO SALUDABLE DE TOLEDO.**

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3-. Comparar la prevalencia tanto de la fragilidad como de la prefragilidad utilizando los CFF con los puntos de corte originales de Linda P. Fried y los CFF con los puntos de corte estandarizados a la población española (S-CFF). Comparar ambos métodos diagnósticos en la predicción de hospitalización, muerte, discapacidad incidente y caídas.

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Los resultados de esta tesis cambian la práctica clínica en el manejo del paciente anciano.

Se autoriza la presentación de la tesis como compendio de publicaciones: SÍ ☐ NO X

Fecha

Firma

RATIFICACIÓN RAZONADA DE LA AUTORIZACIÓN DE DEFENSA DE LA TESIS DOCTORAL POR EL TUTOR

Dª ESTHER LÓPEZ-GARCÍA

Tutora de Dª CRISTINA ALONSO BOUZÓN

en el programa de doctorado RD 1393/2007

A la vista de las razones expuestas en el informe de los Directores de la tesis, se ratifica el referido informe para la autorización de la defensa doctoral presentada por dicha doctoranda.

Fecha:

Firma:

Ratificación del informe por la Comisión Académica del programa de doctorado

El Responsable de la Comisión Académica ratifica, el informe favorable del director de tesis para la autorización de defensa por dicho/a doctorando/a, **una vez que dicha tesis ha sido evaluada positivamente por la Comisión Académica del Programa de Doctorado.**

Madrid, a de de 20

Marque lo que proceda:

□ Programa de doctorado del RD 185/1985 □ Programa de doctorado del RD 778/1998	□ Director del Departamento Correo electrónico: …	
	□ Director en funciones Correo electrónico: …	
	□ Subdirector Correo electrónico: …	Fdo.: ….
□ Programa de doctorado del RD 56/2005 □ Programa de doctorado del RD1393/2007	□ Coordinador del programa Correo electrónico: …	Fdo.: ….
□ Programa de doctorado del RD 99/2011	□ Responsable de la Comisión Académica Correo electrónico: …	Fdo.: ….

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No me gustaría acabar la tesis sin agradecer a todos los que, de alguna manera, habéis contribuido también en ella:

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A mis compañeros del Servicio de Geriatría; muchísimas gracias a todos por haber vivido juntos millones de jornadas de trabajo. Por haber compartido tantas y tantas cosas… Quisiera agradecer especialmente a Marta Castro por su colaboración, no sólo en el primer artículo de esta tesis, sino también en mil quehaceres más, a lo largo de todos estos años. Gracias a los residentes que habéis pasado por aquí aportando entusiasmo, optimismo e ilusión, muchos de vosotros sois ahora amigos. Y finalmente, gracias también al personal administrativo y de enfermería, especialmente a Juan Carlos, Laura, Puri y Nuria, por compartir con nosotros su día a día.

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Mariam El Assar, investigadora de lujo, por su inestimable ayuda, siempre y con una sonrisa.

A Alberto, Antonio, Elia y Paz, por “echar un cable siempre que hiciese falta”

A mis padres; por vuestro maravilloso ejemplo viviendo la vida con fruición en cada momento, tocase lo que tocase. Por haberme dado la oportunidad de tener todas las herramientas para ser independiente. Ya me habéis dado la mejor herencia…

A mi hermana; por estar ahí, a las duras y a las maduras, compartiendo todos los momentos de la vida.

A todos los amigos y amigas que habéis constituido mi red. A todos los que me habéis acompañado a lo largo de estos años, especialmente a Ara, Raquel, Elena, Sara, Marta, Esther, Tita, Gracia, Macu, Maria Eugenia, Roberto, Hugo y Gerardo.

Gracias a todos por haber hecho posible esta tesis.

Dedicada a mis abuelos.

"We don´t stop playing because we grow old, we grow old because we stop playing"

George Bernard Shaw

ÍNDICE GENERAL:

ACRÓNIMOS Y ABREVIATURAS

ABVD: Actividades Básicas de la Vida Diaria.

ACV ó CVD: Enfermedad CerebroVascular

ADMA: DiMetil Arginina Asimétrica.

AIVD: Actividades Instrumentales de la Vida Diaria.

BIF: Breve Instrumento de Fragilidad.

BMI o IMC: Body Mass Index o Indice de Masa Corporal

CFF: Criterios del Fenotipo de Fragilidad.

CHS: Cardiovascular Health Study.

DALYs: Disability Adjusted Life Years.

DI: Discapacidad Incidente.

IQR: Rango intercuartil.

EAV: Encuesta de Ancianos Vulnerables.

ECV: Enfermedad Cardiovascular

EEUU: Estados Unidos.

EFC: Escala de Fragilidad Clínica.

EFR: Escala de Fragilidad-Robustez.

EPOC: Enfermedad Pulmonar Obstructiva Crónica.

ETES: Estudio de Toledo de Envejecimiento Saludable.

FF: Medida de Fragilidad de Gill.

GH: Growth Hormone.

HR: Hazard ratio

I.Charlson: Índice de Charlson.

IDA: Índice de Déficits Acumulados.

IMC: Índice de Masa Corporal.

M: Media

MEC: MiniExamen Cognoscitivo

NDI: No Discapacidad Incidente.

NO: Óxido Nítrico.

OCDE: Organización de Cooperación y Desarrollo Económicos.

OMS: Organización Mundial de la Salud.

ROS: Especies Reactivas de Oxígeno (Reactive Oxygen Speciaes).

S-CFF: Criterios del Fenotipo de Fragilidad eStandarizado

SD: Desviación estándar

Vm: Velocidad de la marcha.

RESUMEN

La fragilidad es el punto clave en la prevención de la discapacidad y en la promoción del envejecimiento saludable. Sin embargo, a pesar de su trascendencia clínica, no existe consenso sobre una definición conceptual ni operativa. Entender los mecanismos fisiopatológicos que subyacen el desarrollo de la fragilidad, identificando nuevos procesos implicados, podría ayudar a avanzar en la comprensión de este concepto en aras de desarrollar un mejor instrumento que permita detectar la fragilidad en la práctica clínica diaria. Por ello nuestro primer objetivo fue, en el artículo 1, hacer una revisión bibliográfica sobre la fisiopatogenia de la fragilidad, así como de las intervenciones farmacológicas evaluadas, hasta el momento, en su manejo clínico. En el proceso de esta revisión nos llamó la atención el papel del stress oxidativo, factor causal de numerosos procesos patológicos y también de la fragilidad. Sabíamos que las especies reactivas de oxígeno (Reactive Oxygen Speciaes ROS) pueden ser producidas por numerosos sistemas. Causan no sólo daño muscular, favoreciendo el envejecimiento y el desarrollo de sarcopenia sino también disfunción endotelial (el estadio más precoz de la enfermedad aterosclerótica). Existe bibliografía que muestra una relación bidireccional entre la fragilidad y la enfermedad cardiovascular tanto clínica como subclínica, sin embargo, hasta el momento, la relación entre la fragilidad y la disfunción endotelial no ha sido evaluada. Por ello, nos propusimos un segundo objetivo (artículo 2): evaluar la relación entre disfunción endotelial, medida por niveles de DiMetilArginina Asimétrica –ADMA, y fragilidad.

Mientras elaborábamos este segundo objetivo, nos pareció que este trabajo tenía una importante limitación. Para establecer los niveles de fragilidad utilizamos, igual que otros grupos, los Criterios del Fenotipo de Fragilidad (CFF) de Linda P. Fried, con los puntos de corte estandarizados a nuestra población, puntos de corte que no habían sido evaluados en la bibliografía previa. Por ello, en un tercer objetivo, nos propusimos evaluarlos, comparando su

comportamiento en nuestra población con el comportamiento de los puntos de corte originales (artículo tres). Y finalmente, el cuarto y último objetivo de esta tesis fue construir árboles de decisión para los resultados de muerte y desarrollo de nuevas discapacidades (o discapacidad incidente) a cinco años, un instrumento para la toma de decisiones de potencial utilidad en la práctica clínica diaria. Este último objetivo está pendiente de publicación.

El primer objetivo se realizó en dos partes: una revisión narrativa y una revisión sistemática. El resto de objetivos se llevaron a cabo utilizando las bases de datos del Estudio de Envejecimiento Saludable de Toledo, un estudio longitudinal, de base poblacional, tipo cohorte abierta, diseñado para evaluar los determinantes asociados a la fragilidad en sujetos mayores de 65 años.

Las conclusiones de esta tesis son:

La primera; la fragilidad es un proceso multidimensional con múltiples sistemas implicados en el que la composición corporal (cantidad de masa magra y masa grasa) juega un papel central. Hasta el momento, la evidencia es insuficiente para recomendar algún tratamiento farmacológico tanto para el manejo de fragilidad como de la sarcopenia.

La segunda; existe una asociación entre la fragilidad y la disfunción endotelial, lo que refuerza la conocida relación entre la fragilidad y la enfermedad cardiovascular y apoya la hipótesis de un papel relevante del sistema vascular en el desarrollo de la fragilidad desde los estadios más precoces de la enfermedad.

La tercera; la estandarización de los Criterios del Fenotipo de Fragilidad a las características de una población concreta, aumenta su validez como herramienta diagnóstica de fragilidad, ya que mejora su capacidad predictiva de dos maneras:

- Identifica a los sujetos prefrágiles de manera consistente como un grupo intermedio de riesgo entre los individuos robustos y frágiles.

- Hace significativas las diferencias de predicción entre los distintos estadios de fragilidad en un espacio de tiempo más corto.

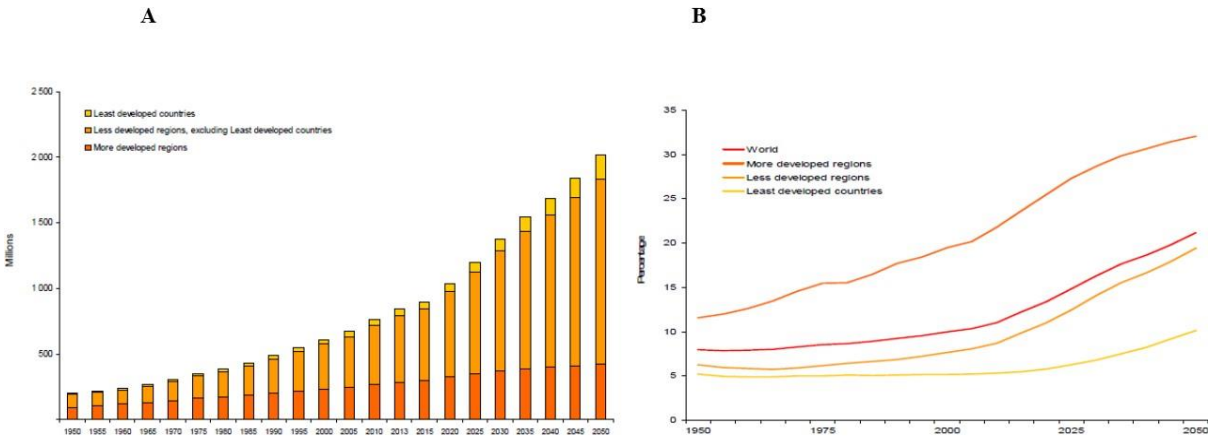
Y la cuarta; nuestros árboles de decisión pueden ser herramientas clínicas de uso sencillo que permiten conocer el riesgo individual de nueva discapacidad y muerte a cinco años, así como detectar subgrupos de pacientes sobre los que podría ser más beneficioso realizar una intervención.

1-. INTRODUCCIÓN

El envejecimiento de la población.

Desde finales del siglo XIX han tenido lugar dos procesos íntimamente relacionados que afectan directamente a la estructura de la población y a su estado de salud. Son la transición demográfica y la transición epidemiológica[1].

La transición demográfica explica el paso desde un régimen demográfico preindustrial, presidido por altas tasas de natalidad y mortalidad, hasta otro postindustrial con bajas tasas, tanto de natalidad como de mortalidad[1]. Inicialmente es la mortalidad materno-perinatal la que disminuye de manera más marcada, para después repartirse de una manera más uniforme entre los diferentes grupos de edad y finalmente, concentrarse en la población anciana[2]. Como consecuencia de estos cambios, se produce un aumento progresivo de la población global y un aumento en la esperanza de vida[2], con un aumento no sólo en el porcentaje sino también en el número absoluto de personas mayores (Figura 1)[3]. Así la población mundial mayor de 60 años se incrementó desde el 8% en 1950 al 12% en 2013 y se prevé que alcanzará el 21% en 2050[3].



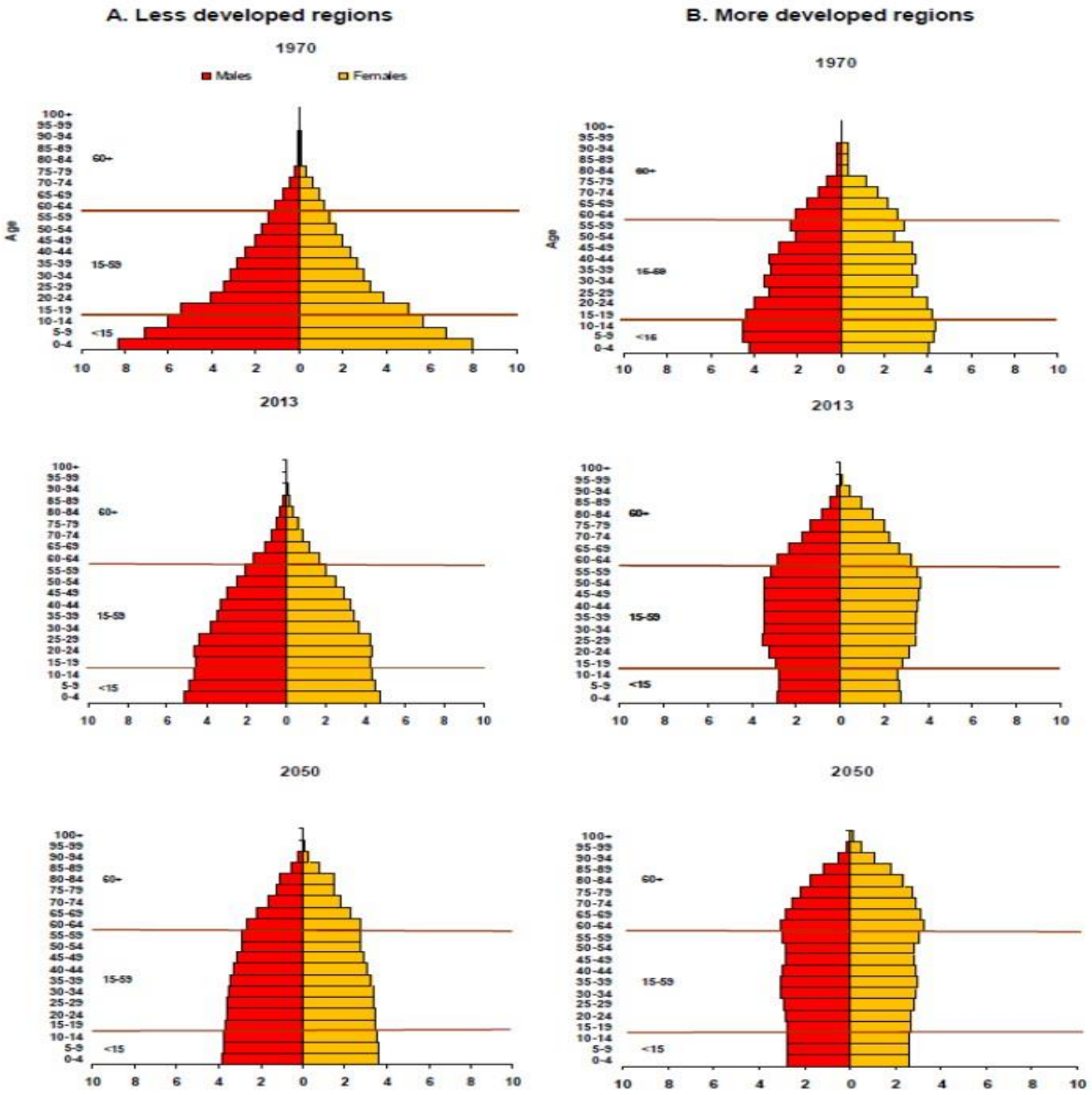
A. Población mayor de 60 años por nivel de desarrollo, 1950-2050.
B. Proporción de población mayor de 60 años: mundial y por nivel de desarrollo, 1950-2050.

Figura 1-. Población mayor de 60 años[3].

Este envejecimiento progresivo de la población está ocurriendo prácticamente en todos los países del mundo. Sin embargo, el ritmo al que se produce es diferente entre ellos, lo que depende fundamentalmente de su nivel de desarrollo[3]. De hecho, cuando comparamos sus datos, estos cambian ligeramente. Así, en los países con mayor nivel de desarrollo, ya en 1950 la población mayor de 60 años alcanzaba el 12%, aumentando al 23% en 2013, previéndose que llegará al 32% en 2050[3].con un destacado protagonismo para los mayores de 85 años, el grupo poblacional que más está creciendo[4]. En los países en vías de desarrollo, la proporción de personas mayores de 60 años se incrementó lentamente entre 1950 y 2013 (del 6 al 9%). Sin embargo, se espera que se acelere este incremento en las próximas décadas alcanzando el 19% en 2050. Los países menos desarrollados, en cambio, han permanecido con una tasa estable de envejecimiento (5% durante muchas décadas) pero, al igual que en el resto de países, se prevé que esta proporción se doble para el año 2050[3]. En resumen, la población de personas mayores está creciendo un 2% cada año, considerablemente más rápido que el porcentaje de crecimiento de la población en general, ritmo que varía en función del nivel de desarrollo del país[5]. Se prevé que en los próximos 25 años, la población anciana continúe con este ritmo de crecimiento: el número de personas mayores de 60 años se doblará en los próximos años, pasando de 841 millones en 2013 a más de 2 billones en 2050[3]. El número de ancianos sobrepasará el número de niños, por primera vez en la historia, en 2047[3].

Estos cambios quedan perfectamente reflejados en la evolución que sufren, con el paso del tiempo, las pirámides poblacionales de los diferentes países (figura 2). Si bien las estructuras han sido completamente diferentes, con los cambios demográficos que se están produciendo, tanto los países con mayor nivel de desarrollo como aquellos con menos, tenderán a tener en

2050, pirámides tubulares muy similares entre sí que representan poblaciones altamente envejecidas[3].



Pirámides de población de países con diferente nivel de desarrollo de 1970, 2013 y 20150.

Figura 2-. Pirámides de población de países con diferente nivel de desarrollo[3].

Paralelamente a la transición demográfica tiene lugar la transición epidemiológica[1]. En un escenario caracterizado por grandes avances económicos y tecnológicos, que ocurren también en el campo de la medicina, la mayor longevidad de los individuos es a la vez causa y consecuencia de los cambios en los patrones de enfermedad[1]. La enfermedad infecciosa (de origen exógeno, transmisible y de curso agudo) disminuye su incidencia, mientras que las enfermedades no transmisibles la aumentan de manera progresiva, convirtiéndose en la causa principal de muerte[5]. Estas enfermedades no transmisibles, endógenas y de curso crónico, se caracterizan por un desarrollo fisiopatogénico muy lento, por lo que las manifestaciones clínicas y la carga de la enfermedad afectan fundamentalmente a las personas mayores. En ellas, con frecuencia coexisten varias de estas enfermedades en un mismo sujeto, dando lugar a lo que se conoce como comorbilidad (figura 3)[5]. Todo esto provoca un cambio radical del panorama médico-sanitario.

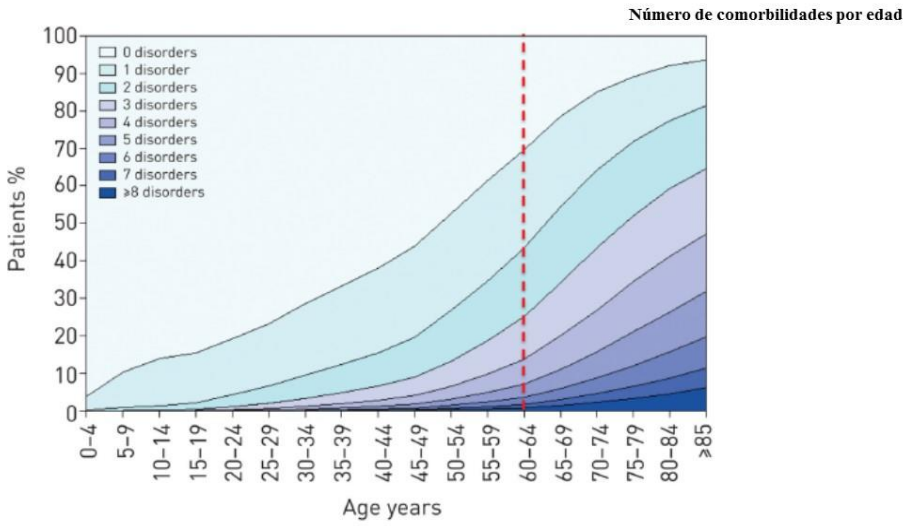


Fig. 3. Número de comorbilidades por edad[5]

Llegados a este punto pudiéramos pensar que el avance de la medicina en los últimos siglos pudiera traducirse, además de en una mayor expectativa de vida, en un mejor estado de salud en estos años de vida adicionales. Sin embargo, la evidencia no refleja eso. La transición epidemiológica trae consigo otro importante cambio: dejamos de estar centrados en la mortalidad como fuerza predominante para hacerlo en la morbilidad, sus secuelas e invalideces[1]. Y esto tiene importantes consecuencias, según muestra la evolución en las últimas décadas de los "Disability Adjusted Life Years" (DALYs), un indicador que combina los años potenciales de vida perdidos y los años vividos con discapacidad[6]. El Global Burden of Disease Study 2013[7] muestra que, desde 1990, el número de DALYs y sus tasas para las enfermedades transmisibles ha disminuido. En cambio, para las enfermedades no transmisibles el número de DALYs han aumentado mientras que las tasas crudas permanecen estables y las tasas estandarizadas por edad también disminuyen[6]. Aunque la salud global está mejorando, el crecimiento de la población y la mayor edad de la misma mantiene las tasas crudas de DALYs constantes[7]. Es decir, son esos años de vida adicionales, cargados de enfermedades no transmisibles con sus secuelas e invalideces, los que mantienen las tasas de DALYs crudas estables. De hecho, el número total de personas en el mundo que viven con discapacidad ha aumentado en un 43% entre 1990-2013, la gran mayoría personas de edad avanzada[7].

Como conclusión a este punto, la transición demográfica y la transición epidemiológica traen como consecuencia poblaciones más envejecidas. La carga de enfermedad (enfermedades no transmisibles, de curso crónico y con discapacidad asociada) se centra en las personas mayores de 65 años[5]. Una carga de enfermedad que lleva aparejada una carga de discapacidad. Llegados a este punto surgen las siguientes preguntas:

¿Es la discapacidad una condición inherente al envejecimiento?

¿El envejecer con discapacidad es evitable o modificable?

Envejecimiento saludable.

El término Envejecimiento Saludable se ha utilizado, a menudo, para referirse a un estado positivo y libre de enfermedades que distingue entre individuos saludables y no saludables[8]. Sin embargo, con el envejecimiento la mayoría de los problemas de salud son el resultado no sólo de la presencia de enfermedades crónicas que coexisten en un mismo sujeto, sino de la interacción de las mismas con el propio proceso de envejecimiento, generando como resultado de dicha interacción una modificación en la capacidad funcional que finalmente repercute en sus hábitos de vida[9]. La capacidad funcional comprende los atributos relacionados con la salud que permiten a una persona ser y hacer lo que es importante para ella[9]. Se compone de la capacidad intrínseca de la persona, las características del entorno que afectan esa capacidad y las interacciones entre la persona y esas características (figura 4)[9].

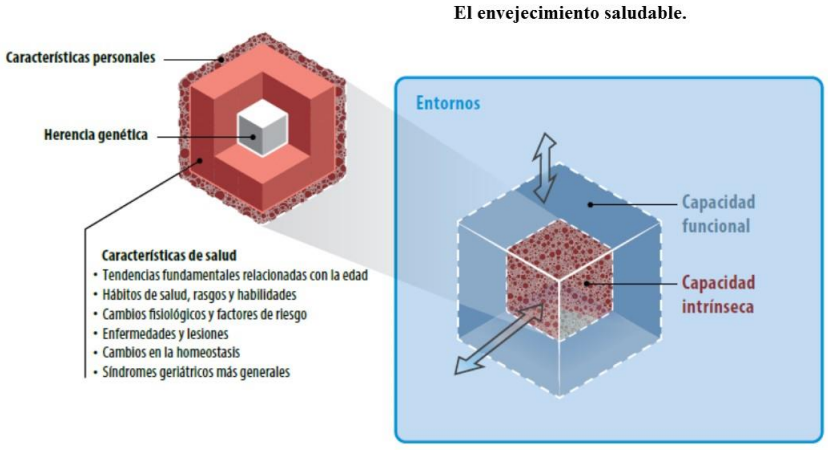


Figura 4-. El envejecimiento saludable[9].

No existe una relación directa entre la presencia de enfermedades, su número y/o gravedad con la capacidad funcional[10] ya que la presencia de enfermedad es sólo una de las

características de salud que influye en la capacidad funcional[9]. Si bien tradicionalmente el trabajo clínico se centra en la enfermedad, existe numerosa evidencia científica que demuestra que la salud de las personas mayores medida en términos de función, y no de enfermedad o grupo de enfermedades, es la que mejor determina la expectativa de vida, la calidad de vida y los recursos o apoyos que precisará cada población[11]. Concordantemente con esto, las evaluaciones funcionales exhaustivas en los ancianos predicen considerablemente mejor la supervivencia y otros resultados (deterioro funcional, hospitalización, institucionalización, caídas, fracturas, etc) que la evaluación de las enfermedades, tanto tomadas de una en una como por el grado de comorbilidad[12, 13]. Por ello, la Organización Mundial de la Salud (OMS), otorga al concepto de Envejecimiento Saludable un sentido mucho más amplio. Desde una definición basada en la ausencia de enfermedades pasa a un concepto basado fundamentalmente en perspectivas funcionales y define el Envejecimiento Saludable como el proceso de fomentar y mantener la capacidad funcional que permite el bienestar en la vejez[9].

En consecuencia, prolongar la expectativa de vida ya no es el objetivo fundamental, y en algunas situaciones puede incluso ser secundario; en la atención sanitaria al paciente anciano el objetivo fundamental es conseguir que estos años de vida adicionales sean saludables, es decir, que se goce de buena salud, entendiendo como tal, según se ha dicho previamente, el mantenimiento de una buena capacidad física y mental que garantice una adecuada calidad de vida[1, 9, 14, 15]. En la actualidad, en la asistencia sanitaria al anciano, la función se ha convertido en el bien supremo a mantener[1].

Para ello, la mejor estrategia es la promoción de la capacidad funcional y el detectar a las personas mayores en riesgo de sufrir discapacidad para intervenir precozmente y evitar el deterioro funcional en vez de intentar recuperar la función una vez que esta ya ha sido perdida[1, 9]. Esta centralización en la prevención se deriva de las siguientes observaciones:

- La primera, diferentes trabajos sugieren que la tasa de discapacidad puede ser modificada en el tiempo[16, 17]. Si bien los resultados que tenemos hasta el momento tienen importantes limitaciones (son escasos, fundamentalmente en países con alto nivel de desarrollo, son numerosos los factores de confusión que influyen en los resultados, la forma de medir la discapacidad es variable, etc) y, por lo tanto, plantean múltiples interrogantes, en diferentes publicaciones se observa una variación temporal de la tasa de discapacidad, lo que apoya la idea de la discapacidad como una cualidad no inherente al envejecimiento[1]. A modo de ejemplo, una evaluación multinacional de la discapacidad leve en países de la Organización de Cooperación y Desarrollo Económicos (OCDE) reveló que había disminuido en algunos países, mientras que había aumentado en otros y había permanecido igual en el resto[18]. Un análisis combinado de grandes estudios longitudinales realizados en países de ingresos altos, efectuado por la OMS en 2014, permitió determinar que la prevalencia de la discapacidad grave (en la que la persona requiere ayuda para realizar actividades básicas) está disminuyendo levemente a pesar de no haberse observado ningún cambio significativo en la discapacidad leve en los últimos 30 años[19].
- La segunda, recuperar la capacidad funcional una vez que la discapacidad está instaurada es bastante improbable. Diferentes trabajos que evalúan la evolución natural de la discapacidad muestran que las transiciones a un mayor grado de discapacidad o a la muerte son mucho más comunes que las mejorías en el grado de discapacidad, las cuales ocurren sólo en un 13.9%[20-22]. Estas recuperaciones ocurrían tras sufrir patologías agudas o accidentes, es decir, cuando la discapacidad es reciente y todavía no está establecida[20].

- Y tercero, existe bibliografía de gran calidad que muestra de manera consistente que es posible prevenir y revertir la discapacidad incipiente interviniendo sobre alguna de las condiciones que aumentan el riesgo o predisponen a ella[23-27]. Este enfoque preventivo nos acerca a una nueva entidad, la fragilidad: un estado biológico de vulnerabilidad que, desde una situación de deterioro funcional es buen predictor de eventos adversos de salud (entre otros, nueva discapacidad y dependencia)[28, 29]. La fragilidad, a diferencia de la discapacidad, es reversible (figura 5). En un trabajo de Gill y colaboradores[30], se demuestra que las transiciones a un mejor estado de fragilidad sucede espontáneamente hasta en un 23% de la población anciana, tasa que puede ser aumentada hasta en un 44% con intervenciones basadas en el ejercicio físico fundamentalmente[25]. Estas transiciones hacia un mejor estado de fragilidad ocurren especialmente en los estadios más leves de fragilidad (prefragilidad)[30].

Figura 5-. La fragilidad en la cascada de la discapacidad y dependencia. Modificada de Martín Lesende y cols[31].

Como conclusión a este punto, la discapacidad no es una condición inherente al envejecimiento o a la enfermedad. Su presencia puede ser modulada. El objetivo de la atención sanitaria a las personas mayores ha cambiado: ya no es conseguir una mayor expectativa de vida sino alcanzar un envejecimiento saludable. Esto es, un envejecimiento centrado en conservar la capacidad funcional. Para ello, parece más eficaz centrar nuestros esfuerzos no en detectar la discapacidad sino en detectar a aquellos sujetos en riesgo de padecerla para intervenir sobre ellos[14, 15, 32].

La fragilidad

El término fragilidad aparece en los años 80, cuando el Consejo Federal en Envejecimiento de Estados Unidos (EEUU) introduce el término de "ancianos frágiles" para referirse a un grupo concreto de la población anciana. Los definen como "personas, usualmente pero no siempre, mayores de 75, que a causa de una acumulación de varios problemas requieren a menudo servicios de apoyo con el fin de hacer frente a la vida diaria"[33]. La fragilidad fue desde el principio un concepto difícil de definir. Ha suscitado múltiples debates y se ha convertido, con el paso del tiempo, en un concepto de marcada relevancia, tanto desde el punto de vista de los cuidados clínicos, como desde la perspectiva de la investigación en envejecimiento[33]. A lo largo de los años, el término ha evolucionado, abarcando diferentes aspectos según los diferentes autores: ser dependiente o estar en riesgo de dependencia, aumento de vulnerabilidad, pérdida de reserva fisiológica, desconexión con el medio ambiente, cronicidad de enfermedad, problemas médicos y psicosociales, presentación atípica de la enfermedad, ser beneficiario potencial de cuidados geriátricos, experimentar un envejecimiento acelerado, etc[34]. Gobbens et al[34] han realizado una revisión en la literatura, narrativa y crítica, de las

definiciones conceptuales y operativas de fragilidad más importantes. Concluyen que una buena definición conceptual de fragilidad debiera incluir los siguientes cinco puntos[34]:

- Aproximación multidimensional: a diferencia de la discapacidad, los hallazgos fisiológicos que caracterizan a la fragilidad no son el resultado de cambios en un único sistema[28]. La fragilidad es un proceso sinérgico, multifactorial y complejo donde los cambios que suceden en el sistema músculo esquelético tienen un papel central[29]. Asumir que la fisiopatogenia de la fragilidad es multidimensional marca las bases para alejarnos de un enfoque clínico basado en el órgano o en la enfermedad, para centrarnos en un abordaje integral basado en la salud[35], entendiendo la salud como el mantenimiento de la capacidad funcional. Por lo tanto, la definición ideal de fragilidad debiera incluir los diferentes dominios del funcionamiento humano[34].
- Estado dinámico: la fragilidad es un continuum, resultado de la interacción entre factores personales (cognitivos, físicos, psicológicos y espirituales) y ambientales (económicos, sociales, legales e institucionales)[36, 37]. En este continuum se puede transitar de manera espontánea hacia estados más severos de fragilidad o, en menos casos (un 23%), hacia un estado de mayor robustez[30]. Estas transiciones hacia un estado clínico mejor ocurren con mayor probabilidad en estadios más leves de fragilidad[30]. Por ello, la definición ideal de fragilidad debiera identificar diferentes grados clínicamente reconocibles [34].
- Predice resultados adversos: la fragilidad refleja un aumento de vulnerabilidad asociado a la edad[38] y, por lo tanto, debe ser marcador de esos individuos vulnerables que están en alto riesgo de sufrir resultados adversos[34]. En este sentido el concepto ideal de fragilidad sería aquel que pudiese ser validado en su capacidad

predictora[39]. Sin embargo, puesto que no hay "gold standard" con las que las definiciones operativas de fragilidad puedan ser comparadas, un concepto adecuado de fragilidad sería aquel que tiene una fuerte validez predictiva y las bases de esta validez pueden ser entendidas[39].

- No incluye la enfermedad, la comorbilidad o la discapacidad (aunque a veces coexista con ella): la fragilidad debe ser diferenciada de la comorbilidad y la discapacidad aunque a veces estos tres conceptos se solapen[40]. La relación entre fragilidad y enfermedades crónicas es muy compleja y muy poco entendida[35]. El desarrollo de enfermedades puede precipitar el desarrollo de fragilidad porque estas necesitan el organismo para movilizar fuentes de energía disponibles con la potencial consecuencia de consumir reserva funcional del organismo sobre el que actúan[35]. La discapacidad también exacerba la fragilidad[34]. Sin embargo, aunque fragilidad, comorbilidad y discapacidad están íntimamente relacionadas, no siempre coexisten en el mismo sujeto[40] y, por lo tanto, considerarlas sinónimos constituye un grave error conceptual. De hecho, en el clásico estudio de Fried et al en sujetos de la cohorte del Cardiovascular Health Study, el 68% de los ancianos frágiles tenían dos o más enfermedades crónicas y, sólo el 27% tenían discapacidad[40]. En este sentido, algunos autores definen la fragilidad como un estado de prediscapacidad[14, 41].
- Debe ser factible de aplicar (practicable): la definición conceptual ideal de fragilidad debería servir como base para desarrollar un instrumento con el que detectar y medir la fragilidad[34] e incluir aspectos sobre los que las intervenciones preventivas pudiesen actuar[37]. Es decir, debiera ser sensible clínicamente[39] y aceptada por aquellos que la utilizarán en su práctica diaria[34].

Ninguno de los conceptos de fragilidad desarrollados hasta el momento incluyen estos cinco puntos y, por lo tanto, no existe consenso sobre cuál es la mejor definición de fragilidad para su uso clínico[28, 34, 41]. En 2013, se publicó una declaración de consenso, realizada mediante el método Delphi, que buscaba una definición de fragilidad[28]. Llegar a esa definición no fue posible. Sin embargo, más del 80% de los expertos estuvieron de acuerdo en que los cinco puntos previos eran características inherentes a la fragilidad[28]. Puesto que no existe una definición conceptual aceptada por todos los profesionales ¿cuáles son aquellas más destacadas?

Tras la primera definición de fragilidad dada por el Consejo Federal de Envejecimiento de EEUU en 1978[33], Winograd (1991) define la fragilidad como un estado ni "demasiado independiente" ni "demasiado deteriorado" que pone a la persona en riesgo de efectos adversos[42]. Partiendo de la definición de Buchner y Wagner (1992)[43] que definían la fragilidad como un estado caracterizado por una reserva fisiológica disminuida que asociaba un incremento de la susceptibilidad a la discapacidad, el mismo grupo evolucionó a un concepto más completo en 1997. Fueron Campbell y Buchner los que incluyen la naturaleza multidimensional de la fragilidad y sitúan al sujeto en un estado de vulnerabilidad o de alto riesgo que le predispone, ya no solo a discapacidad, sino a toda clase de resultados adversos ante pequeñas situaciones de stress[44]. Denominan la fragilidad como la "discapacidad inestable"[44]. Siguiendo con esta línea de pensamiento, finalmente Linda P. Fried y colaboradores (2001) dan la definición más completa de fragilidad: es el síndrome biológico, asociado a la edad, caracterizado por una disminución de la reserva funcional y de la resistencia frente a diferentes factores de stress y que resulta del deterioro de múltiples sistemas, causando vulnerabilidad para sufrir resultados adversos[29].

Frente a la línea previa marcada por la disminución de la reserva funcional, Rockwood publica, por primera vez en 1994[45], su definición de fragilidad basada en la acumulación de déficits. Comienza definiendo la fragilidad como "el estado de vulnerabilidad resultado de un disbalance entre los activos que mantienen la salud y los déficits que la amenazan". Hammerman continúa con esta línea del desequilibrio, pero profundiza un poco más buscando una relación entre los mecanismos clínicos y biológicos de la fragilidad, que es definida como una "compleja y acumulativa expresión de respuestas homeostáticas alteradas a factores de stress múltiples que resultan en un disbalance metabólico"[46].

Partiendo de estos diferentes conceptos de fragilidad surgen distintas definiciones operacionales o instrumentos para detectarla[34]. En una revisión sistemática reciente[47] se detectaron 67 instrumentos para evaluar la fragilidad. De ellos, nueve fueron citados en más de 200 trabajos. Estos nueve instrumentos, de mayor a menor número de citaciones son[47]:

- Criterios del Fenotipo de Fragilidad (CFF)[29], citado en 1891 ocasiones;
- Índice de Déficits Acumulados (IDA)[48], citado 401 veces;
- Medida de Fragilidad Física de Gill (FF) o Physical Frailty Score[49], 254 veces;
- Evaluación de Fragilidad/Robustez (EFR)[50], 246 veces;
- Escala de Fragilidad Clínica (EFC)[51], 239 veces;
- Breve Instrumento de Fragilidad (BIF)[52], 226 veces;
- Encuesta de Ancianos Vulnerables (EAV)[53], 225 veces;
- Escala FRAIL[41]; 211 veces;
- y el Instrumento de Screening de Winograd[42], 198 veces.

En la revisión sistemática de Buta et al[47] se evalúa qué características, de las identificadas por Gobbens[34] como puntos indispensables en el concepto de fragilidad, están incluidas en cada

una de los instrumentos previos. Los resultados de esta revisión sistemática se sintetizan en la tabla 1.

Conceptos básicos de fragilidad incluidos en los instrumentos diagnósticos más citados en la literatura

Conceptos básicos	CFF	IDA	FF	EFR	EFC	BIF	EAV	FRAIL	Winograd
Multidimensional	No	Si	No	Si	Si	Si	Si	No	Si
Dinámico (no linear)	Si	No	No	No	No	No	No	Si	No
Predice outcomes	Si	Si	Si	No	Si	Si	Si	No	Si
Excluye comorbilidad	Si	No	Si	Si	No	No	Si	No	No
Excluye discapacidad	Si	No	Si	No	No	No	No	Si	No
Es practicable	Si	Si	No	No	Si	Si	Si	No	No

CFF: Criterios del Fenotipo de Fragilidad. **IDA:** Índice de Déficits Acumulados. **FF:** Medida de Fragilidad Física. **EFR:** Evaluación de Fragilidad/Robustez. **EFC:** Escala de Fragilidad Clínica. **BIF:** Breve Instrumento de Fragilidad. **EAV:** Encuesta de Ancianos Vulnerables. **FRAIL:** Escala Frail. **Winograd:** Instrumento de Screening de Winograd.

Tabla 1-. Conceptos básicos de fragilidad incluidos en los instrumentos diagnósticos más citados en la literatura.

Como podemos ver los CFF es, de los instrumentos más citados en la bibliografía, el instrumento que respeta mayor número de las características básicas de una buena definición conceptual de fragilidad[47]. Incluye cinco criterios que son: la pérdida de peso, la debilidad muscular, la lentitud, la sensación de agotamiento y la poca actividad física. Los sujetos que cumplan 3 o más criterios son frágiles, los que cumplan 1 o 2 son prefrágiles y si no cumplen ninguno son robustos[29]. Los CFF, no solo es el instrumento más citado en la literatura, sino que además ha sido el instrumento utilizado para mayor número de usos diferentes: para evaluación de riesgo de efectos adversos (caídas, institucionalización, muerte, hospitalización, etc), en estudios metodológicos, en estudios etiológicos de fragilidad, en estudios de biomarcadores, como criterios de inclusión/exclusión, para estimar la prevalencia de la fragilidad y para la toma de decisiones clínicas[47]. Es decir, ha demostrado ser "practicable".

Es un instrumento que excluye de sus criterios la comorbilidad y la discapacidad y respeta el concepto de dinamismo no lineal como han demostrado Gill y colaboradores[30].

Sin embargo, los CFF tienen dos limitaciones importantes[54]. La primera, realiza una aproximación al concepto de fragilidad centrado en un papel muy marcado del sistema musculoesquelético sin tener en cuenta otros dominios de la fragilidad, por ejemplo, la cognición, la afectividad, los órganos sensoriales, etc[54]. La segunda, si bien es el instrumento más utilizado y más evaluado, la mayoría de estos usos se han realizado en el ámbito de la investigación epidemiológica, estando el ámbito clínico apenas explorado[47]. Es decir, aunque los CFF es el instrumento más evaluado, más citado y que se ajusta a mayor número de requerimientos de una buena definición conceptual de fragilidad, esto no es suficiente para su recomendación incondicional[47].

En conclusión, a este último punto de la introducción; si bien la fragilidad es el punto clave en la prevención de la discapacidad y en la promoción del envejecimiento saludable, no existe una definición conceptual ni operativa que haya logrado el salto definitivo a la práctica clínica. Entender los mecanismos fisiopatológicos que subyacen el desarrollo de la fragilidad, identificando nuevos procesos implicados, podría ayudar a avanzar en la comprensión de este concepto en aras de desarrollar un mejor instrumento que permita detectar la fragilidad en la práctica clínica diaria.

2-. OBJETIVOS

El **Objetivo 1** de esta tesis fue hacer una revisión bibliográfica de los mecanismos fisiopatológicos que subyacen el desarrollo de fragilidad, así como de las intervenciones farmacológicas evaluadas, hasta el momento, para el manejo clínico de la fragilidad. Este objetivo se desarrolla en el artículo titulado: "Pharmaceutical interventions for frailty and sarcopenia". Este artículo ha sido publicado en: Current Pharmaceutical Design. 2014;20(18):3068-82.

Con el **Objetivo 2** quisimos profundizar en la fisiopatología de la fragilidad. Para ello nos propusimos evaluar la relación entre disfunción endotelial, medida por niveles de DiMetilArginina Asimétrica –ADMA-, y fragilidad. Este segundo objetivo se desarrolla en el artículo 2 titulado: "Association between endothelial dysfunction and frailty: the Toledo Study for Healthy Aging." Este artículo ha sido publicado en: Age (Dordr). Feb 2014; 36(1):495-505.

Como **Objetivo 3** de esta tesis nos propusimos comparar la prevalencia, tanto de fragilidad como prefragilidad, utilizando los CFF con los puntos de corte originales de Linda P. Fried y los CFF con los puntos de corte estandarizados a la población española (S-CFF). Además quisimos comparar ambos métodos diagnósticos en la predicción de hospitalización, muerte, discapacidad incidente y caídas. Este objetivo se desarrolla en el artículo titulado: "The standarization of frailty phenotype criteria improves its predictive ability. The Toledo study for healthy aging.". En JAMDA 2017, 2. pii: S1525-8610(16)30520-5. doi: 10.1016/j.jamda. 2016.11.003. (Epub ahead of print).

Finalmente, el **objetivo 4** de la tesis fue construir árboles de decisión para los resultados de muerte y desarrollo de nuevas discapacidades (o discapacidad incidente) a cinco años, un instrumento para la toma de decisiones de potencial utilidad en la práctica clínica diaria.

3- METODOLOGÍA

Para desarrollar el objetivo 1, metodológicamente realizamos en primer lugar una revisión narrativa de los mecanismos fisiopatológicos que subyacen a la fragilidad explorando de manera detenida la relación entre sarcopenia y fragilidad. Para desarrollar la segunda parte de este objetivo, realizamos una revisión sistemática de todos los ensayos clínicos que evalúan intervenciones exclusivamente farmacológicas, realizados en sujetos ancianos, para prevenir o tratar tanto la sarcopenia como la fragilidad. La búsqueda se realizó utilizando EMBASE, CINAHL, MEDLINE, Cochrane, Pubmed y otras bases de datos electrónicas. Se buscaban ensayos clínicos aleatorizados, realizados en personas mayores (por encima de 60 años), publicados hasta mayo de 2013. Los términos utilizados fueron: ("Fragilidad" o "Frail" o "Sarcopenia") y ("Angiotensin Converting Enzyme (ACE) Inhibitors" o "ACE Inhibitors" o "Vitamin D" o "Testosterone" o "Dehydroepidiosterone (DHEA)" o "DHEA" o "Growth Hormone (GH)" o "GH" o "Estrogens" o "Sex Esteroids" o "Insulin Like Growth Factor-1 (IGF-1)" or "IGF-1"). No hubo límites en la búsqueda de idioma. Las citas de todos los artículos propuestos fueron revisadas para identificar otros estudios que incluir en la revisión.

Los criterios de selección fueron: a) Ensayos clínicos aleatorizados, b) realizados en población mayor de 60 años, c) evaluaban intervenciones exclusivamente farmacológicas, d) el outcome principal era fragilidad y/o sarcopenia.

Se consideraron criterios de exclusión: a) incluir en la intervención medidas no farmacológicas como el ejercicio y/o la nutrición, b) utilizar outcomes intermedios como medida de fragilidad o sarcopenia.

Para desarrollarlos objetivos 2, 3 y 4, recurrimos al *Estudio de Toledo de Envejecimiento Saludable (ETES).* El ETES es un estudio longitudinal, de base poblacional, tipo cohorte abierta, diseñado para evaluar los determinantes asociados a la fragilidad en sujetos mayores

de 65 años, institucionalizados (1.9%) y no institucionalizados (98.1%), tanto del ámbito urbano como rural. Los objetivos principales del estudio son:

1. Identificar qué factores biológicos, psicológicos y sociales favorecen un envejecimiento en salud.
2. Examinar qué factores: sociales, funcionales, de comorbilidad, mentales, alimentarios, de rendimiento físico, biológicos y genéticos predicen la aparición de fragilidad, discapacidad, deterioro cognitivo y mortalidad.
3. Determinar la relación entre fragilidad y enfermedad vascular.
4. Determinar el papel de los cambios inflamatorios y hormonales como facilitadores de discapacidad y precipitantes de eventos - principalmente vasculares- en los ancianos.
5. Medir el impacto que tienen la comorbilidad, la discapacidad y la fragilidad en el sistema de salud

Los sujetos participantes en el ETES proceden de dos fuentes:

- La primera, de una "cohorte histórica" formada por los supervivientes de un estudio previo (El Estudio de Toledo). Estos sujetos eran mayores de 77 años en el 2006.
- La segunda, la "nueva cohorte" son sujetos de entre 65-76 años en 2006, especialmente reclutados para el ETES.

Todos los participantes fueron seleccionados mediante un muestreo aleatorio polietápico, tomando como base el padrón municipal y los censos electorales de Toledo. Hasta el momento se han realizado tres evaluaciones a lo largo del tiempo (tres cortes u oleadas): la primera evaluación se realizó durante los años 2006-2009, la segunda entre 2011-2013 y la tercera se está realizando actualmente (2015-2017).

En la primera evaluación (2006-2009), se valoraron a 2.488 personas mayores de 64 años, en tres fases diferentes. La primera parte fue una entrevista puerta a puerta realizada por psicólogos, de 90 minutos de duración, que constaba de datos sociodemográficos, comorbilidad y tratamiento actual, evaluación funcional (valoración de la dependencia y neuropsicológica -cognitiva y afectiva-), evaluación nutricional, social y de calidad de vida. La segunda, tres equipos de enfermería, previa cita, se desplazaron al domicilio de los sujetos para realizar una exploración física completa: medidas de antropometría, tomas de tensión arterial y frecuencia cardiaca, pruebas de función respiratoria, electrocardiograma, cribado de arteriopatía periférica mediante doppler, pruebas de limitación funcional (medidas basadas en la ejecución) y un cribado de síntomas cognitivos y de incontinencia urinaria. Y la tercera parte en la que los sujetos se desplazaron a su centro de salud para la extracción de muestras sanguíneas para su análisis y almacenamiento.

En las siguientes evaluaciones se utilizó información del Instituto Nacional de Estadística (Base de Datos Nacional sobre Mortalidad) para evaluar la mortalidad. Las hospitalizaciones fueron detectadas utilizando la base de datos del Complejo Hospitalario de Toledo y mediante seguimiento telefónico. Seguimiento medio de 5.5 años (rango 0.3-6.79 años). Se definió el desarrollo de nuevas discapacidades o la existencia de discapacidad incidente, cuando existía una transición de capaz a discapaz de alguno de los Items del indice de Katz y se consideró no discapaz incidente, al que no vario su condición en ninguno de los items de la escala. Para detectar la discapacidad incidente y las caídas (haber sufrido al menos una caída en el año previo) se le preguntó directamente al sujeto mediante nueva entrevista presencial. Media de seguimiento de 5.02 años (rango 4.8-5.2 años).

El protocolo del estudio fue aprobado por el Comité Ético de Investigación Clínica del Complejo Hospitalario de Toledo. Todos los participantes fueron completamente informados y firmaron el consentimiento informado previamente a ser incluidos en la cohorte.

Los análisis estadísticos realizados están descritos en el anexo correspondiente a la publicación. En el caso concreto del objetivo 4 (no publicado), se utilizó un método de particiones recursivas utilizando el SPSS v22. El particionamiento recursivo es una técnica de análisis multivariante que detecta aquellas variables explicativas que clasifican los eventos de la manera más efectiva. Con estas variables, forma árboles de decisión clínica. Para ambos resultados (muerte y discapacidad inicidente) las variables explicativas que se incluyeron en el análisis fueron: edad, sexo, diabetes mellitus, hipertensión arterial (HTA), deterioro cognitivo, depresión, enfermedad cerebrovascular (ACV), enfermedad cardiovascular (ECV), enfermedad pulmonar obstructiva crónica (EPOC), cáncer, comorbilidad, polifarmacia, velocidad de la marcha (vm), fragilidad, caídas y discapacidad. Las características demográficas y la comorbilidad fueron recogidas por psicólogos entrenados, que detectaron la presencia o ausencia de las diferentes enfermedades por preguntas directas al sujeto, en base a informes médicos y/o por estar en tratamiento farmacológico para esa patología. La comorbilidad fue medida utilizando el Índice abreviado de Charlson (I. Charlson). La presencia de deterioro cognitivo fue considerada positiva cuando el MiniExamen Cognoscitivo (MEC) era ≤18. Para la presencia de depresión se utilizó la escala GDS-15 (≤5). La velocidad de la marcha se midió sobre 3m, al paso habitual, sin velocidad de arranque ni deceleración. La presencia de fragilidad se midió utilizando los S-CFF. Se definió la presencia de caídas como haber sufrido al menos una caída en el último año.

4-. MECANISMOS FISIOPATOLÓGICOS QUE SUBYACEN LA FRAGILIDAD. INTERVENCIONES FARMACEUTICAS

El primer objetivo de esta tesis fue hacer una revisión de los mecanismos fisiopatológicos conocidos que subyacen la fragilidad así como las intervenciones farmacológicas desarrolladas y evaluadas hasta el momento en base a esos mecanismos. Este objetivo se desarrolla en el artículo titulado: “Pharmaceutical interventions for frailty and sarcopenia” (ver anexo II de esta tesis).

Los hallazgos fisiológicos que caracterizan a la fragilidad no son el resultado de cambios en un único sistema. Por el contrario, la fragilidad es un proceso sinérgico, multifactorial y complejo donde los cambios que suceden en el sistema músculo esquelético tienen un papel central. De tal manera que la sarcopenia (o pérdida de masa muscular asociada a la edad) es considerada un componente importante en el desarrollo de fragilidad.

Factores músculoesqueléticos

La pérdida relacionada con la edad del tejido corporal magro (lean body mass, LBM) o la masa muscular asociada a un mal funcionamiento se conoce como sarcopenia. Al igual que ocurre con el hueso, se gana masa muscular (en función de los hábitos de vida especialmente nutrición y ejercicio) hasta los 30-35 años, en que se alcanza el pico de masa muscular. A partir de entonces, se pierde masa muscular de manera progresiva, hasta que en edades muy avanzadas, dependiendo del punto de partida (pico de masa muscular) y la tasa de pérdida de masa muscular se darán los diferentes síntomas clínicos. Los principales mecanismos subyacentes a la sarcopenia son:

Diversos cambios a nivel celular (la apoptosis o muerte celular programada producida a través de vías de señalización controladas que dan como resultado la autodestrucción celular sin ningún daño al tejido circundante, la disfunción mitocondrial con el concomitante decrecimiento en la producción de ATP mitocondrial en el músculo así como el stress oxidativo que regula las vías de señalización sensibles al redox, aumentan la expresión de los

genes catabólicos y activan las vías apoptóticas contribuyendo así a la progresión de la sarcopenia se traducen a nivel tisular en tres cambios morfologicos importantes:

- pérdida de motoneuronas y con un remodelado de las unidades motoras mediante la reinervación colateral;
- deterioro de la activación neuromuscular y,
- patrones no coordinados de activación neuronal intermuscular.

Estos tres cambios dan lugar a una estimulación neuronal reducida que ocurre paralelamente a una disminución progresiva del área de la sección transversal de la fibra muscular, siendo las fibras de tipo II las que están principalmente involucradas. Las restantes fibras de tipo II parecen mantener su eficiencia probablemente ajustando su capacidad para producir energía, como lo sugiere la ausencia de cambios relacionados con la edad en las actividades enzimáticas de la maquinaria anaeróbica para la producción de energía. Estos cambios estructurales dan como resultado una función muscular más pobre y una disminución de la fuerza y potencia, que se traducen también a nivel clínico como una velocidad de la marcha reducida o menor capacidad para hacer actividad física, constituyendo estos síntomas core central en el diagnóstico de fragilidad (criterios L.P Fried)

Pero además de lo que ocurre en el músculo, en la fisiopatogenia de la sarcopenia tambien influye lo que está pasando a nivel sistémico. La disregulación de las citoquinas catabólicas (implicado en el desarrollo de la sarcopenia debido su papel en la reducción de la síntesis de proteínas musculares), la pérdida de la producción de hormonas que ocurre durante el envejecimiento, especialmente las hormonas anabólicas (hormonas sexuales, GH, IGF-1) y la influencia de factores externos como la desnutrición, el estilo de vida sedentario y las enfermedades crónicas son factores implicados en el desarrollo de sarcopenia.

Pero, como hemos mencionado previamente, la sarcopenia no es el único mecanismo en producir sarcopenia, sino que representa solamente una dimensión del complejo síndrome geriátrico de la fragilidad. Junto con la sarcopenia, e interactuando con ella, los siguientes factores están involucrados en el desarrollo de fragilidad:

1-. Cambios endocrinos: los cambios hormonales asociados a la edad afectan a la composición corporal y favorecen la pérdida de masa muscular en ancianos frágiles.

2-. Efectos de la inflamación: la activación del proceso de inflamación y de la cascada de coagulación aumentan con la edad, pero también son asociados independientemente con el desarrollo de fragilidad. Respecto a la etiología de la fragilidad, se ha hipotetizado que la inflamación puede ser una causa primaria, una respuesta a alguna noxa o infección o parte de algún otro proceso fisiopatológico asociado con la disregularización celular, nuclear, transcripcional y/o otros controles homeostáticos.

3-. Nutrición: la ingesta proteica es de interés en la fragilidad. Debido a cambios existentes en la cinética proteica y al aumento del turnover hay evidencia de unos requerimientos aumentados de la ingesta diaria de proteínas (1-1.5g/Kg/d) (68)

4-. Estrés oxidativo: el estrés oxidativo es un conocido factor causal de numerosos procesos patológicos. Hay diferentes sistemas propuestos como fuentes de Especies de Oxígeno Reactivas (Reactive Oxygen Speciaes, ROS) que son: NADPH oxidasa, xantina oxidasa, NO sintasa y cadena respiratoria mitocondrial. Junto con el estrés oxidativo generado por la célula muscular, otras fuentes potenciales de ROS son los generados por la microvasculatura. Este estrés oxidativo es uno de los orígenes de la disfunción endotelial microvascular que acompaña el envejecimiento en gente sin enfermedad cardiovascular o factores de riesgo cardiovasculares. La presencia de disfunción endotelial podría estar involucrada en la disminución del suministro capilar de tejidos observado en el músculo viejo. *De aquí surge*

nuestra segunda hipótesis: la disfunción endotelial juega un papel fisiopatológico en el desarrollo de la fragilidad.

Como se ha manifestado a lo largo del texto, muchos de los factores relacionados con la fragilidad son muy difíciles de separar fisiopatológicamente unos de otros. Factores hormonales, inmunológicos, nutricionales, musculares, vasculares, etc, han sido involucrados en este proceso, siendo, como hemos visto, la composición corporal su factor central. En presencia de sarcopenia se favorece y perpetúa la cascada fisiopatológica de la fragilidad, no solo mediante sus mecanismos tisulares y sistémicos sino también por la disminución en la reserva energética que favorece la falta de respuesta a estresores como enfermedades agudas. Hasta el momento las dianas terapéuticas farmacológicas propuestas y evaluadas para el manejo de la fragilidad son, fundamentalmente, factores hormonales que actúan a nivel osteomuscular. El número de ensayos clínicos realizados son escasos, metodológicamente tienen importantes limitaciones ya que con frecuencia utilizan resultados intermedios, son frecuentes los resultados negativos o con escasa trascendencia clínica y, en general, son trabajos de escasa potencia (ver anexo II). En el momento de la publicación del artículo en el que se desarrolló este objetivo (anexoII), la testosterona se presentaba como una posible opción terapéutica ya parecía haber demostrado una mejora de las medidas basadas en la ejecución y un aumento de la masa muscular en diferentes trabajos[55-57], además de sugerir beneficios para la prevención de fracturas[58] y la mejora del deterioro cognitivo[59]. Trabajos posteriores aportan resultados negativos[60], lo que junto a la alta tasa de efectos secundarios, especialmente a nivel cardiovascular[61, 62], hacen desaconsejable su uso. Por lo tanto, podemos afirmar que, hasta el momento, en base a la evidencia existente no existe tratamiento farmacológico eficaz y seguro para el tratamiento de la fragilidad y de la sarcopenia.

Sin embargo, aunque este camino no ha resultado fructífero, seguir trabajando en un mayor entendimiento del proceso fisiopatológico de la fragilidad es una vía para poder seguir planteándonos nuevas dianas terapéuticas sobre las que intervenir. En este sentido, como ya hemos comentado, nos llamó la atención el papel del stress oxidativo como factor causal de numerosos procesos patológicos y también de la fragilidad[63]. Las especies reactivas de oxígeno (Reactive Oxygen Speciaes ROS) pueden ser producidas por numerosos sistemas[63]. Causan no sólo daño muscular, estimulando los efectos apoptóticos de diferentes factores locales favoreciendo así procesos como el envejecimiento y el desarrollo de sarcopenia[64], sino también disfunción endotelial (Figura 6)[63]. La disfunción endotelial, el estadio más precoz de la enfermedad aterosclerótica que precede a la enfermedad cardiovascular, juega un papel fisiopatológico en el proceso del envejecimiento[65]. Existe bibliografía que muestra una relación bidireccional entre la fragilidad y la enfermedad cardiovascular tanto clínica como subclínica[66], sin embargo, hasta el momento, la relación entre la fragilidad y la disfunción endotelial no ha sido evaluada.

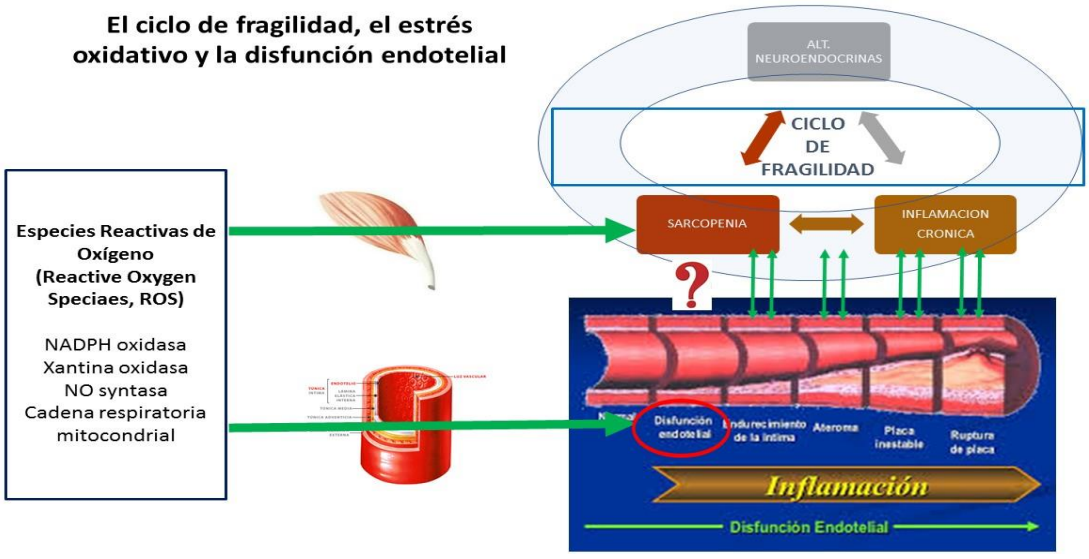


Figura 6-. El ciclo de la fragilidad, el stress oxidativo y la disfunción endotelial (elaboración propia).

5-. LA DISFUNCIÓN ENDOTELIAL Y LA FRAGILIDAD

El segundo objetivo de esta tesis evalúa la relación entre disfunción endotelial, medida por niveles de DiMetilArginina Asimétrica –ADMA-, y fragilidad. Este segundo objetivo se desarrolla en el artículo 2 titulado: "Association between endothelial dysfunction and frailty: the Toledo Study for Healthy Aging." Este artículo ha sido publicado en: Age (Dordr). Feb 2014; 36(1):495-505 (anexo III de esta tesis)

Resultados:

Población de estudio

La población incluida en este estudio estaba compuesta por mil doscientas ocho personas (552 hombres y 735 mujeres). La edad media fue 74.4 (5.4) años. Las características de la muestra en función del estado de fragilidad así como los niveles de ADMA según las características de los sujetos se encuentra detallado en el anexo III de esta tesis. El 18.8% de los sujetos fueron diabéticos, el 52.1% tenían hipertensión, el 39.0% tenían hipercolesterolemia y el 41.4% eran obesos. Respecto a la presencia de enfermedades ateroscleróticas, 401 sujetos estaban diagnosticados de angor, infarto de miocardio, ictus y/o claudicación intermitente. Las mujeres padecían más comorbilidades que los hombres 1.7 (SD=1.1) versus 1.4 (SD=1.1), $p<0.0001$. La fragilidad fue asociada con la edad ($p<0.0001$), el bajo nivel educacional ($p=0.002$), BMI ($p<0.0001$), y la presencia de enfermedad aterosclerótica ($p<0.0001$).

Cuando evaluamos los niveles de ADMA según las características de los sujetos tabla 2, anexo III), encontramos diferencias en los valores de ADMA en función de los estados de fragilidad ($p=0.045$) así como en función de la edad, el sexo y el nivel educacional. No hubo asociación con los factores de riesgo clásicos ni con la enfermedad cardiovascular clínica.

Efecto de la disfunción endotelial en la relación entre ADMA y fragilidad.

Encontramos una interacción entre los niveles de ADMA y la enfermedad aterosclerótica en el riesgo de fragilidad (p=0.045). En los sujetos sin enfermedad aterosclerótica clínica, la media de los niveles de ADMA fueron significativamente más alto en sujetos frágiles que en prefrágiles o robustos [M=0.83 (SD=0.26), M=0.77 (SD=0.26) y M=0.78 (SD=0.23) respectivamente, p para la diferencia= 0.032]. En cambio, en sujetos con enfermedad aterosclerótica clínica no encontramos ninguna relación estadísticamente significativa (p=0.324) (Figura 1, anexo III).

Para evaluar la relación entre la disfunción endotelial y la fragilidad, realizamos análisis multivariantes en sujetos con enfermedad cardiovascular y sin ella, por separado. Después de ajustar por los factores de riesgo clásicos, encontramos un incremento significativo del riesgo de fragilidad asociado con un incremento de los niveles de ADMA (p para la tendencia = 0.032) en sujetos sin enfermedad cardiovascular clínica. Esta tendencia no fue hallada en los sujetos con CVD (Tabla 3, anexo III). Ajustes posteriores con el Índice Tobillo-Brazo, una medida objetiva de enfermedad aterosclerótica subclínica, no modificaron sustancialmente estos resultados. El riesgo de ser frágil se incrementaba con el incremento de los niveles de ADMA, siendo el doble para los sujetos en el cuartil más alto [2.09, 95% CI (0.95-4.61), p para la tendencia=0.018] (Tabla 3, anexo III). Finalmente, puesto que los niveles de ADMA pueden ser modificados por la presencia de insuficiencia renal, hicimos un último ajuste en función de los niveles de creatinina. Este último ajuste no produjo ningún cambio significativo en la tendencia de la asociación [2.05, 95% CI (0.92-4.51), p para la tendencia=0.021] (Table 3). De nuevo, no se encontró asociación en los sujetos con enfermedad cardiovascular. No encontramos ninguna interacción significativa entre otras características de los sujetos y los niveles de ADMA en el riesgo de ser frágil.

Discusión:

Este es el primer trabajo que muestra una asociación entre la fragilidad y la disfunción endotelial. Estos resultados no solo refuerzan la conocida relación entre la fragilidad y la enfermedad cardiovascular sino que apoyan la hipótesis de un papel relevante del sistema vascular en el desarrollo de la fragilidad que estaría implicado desde los estadios más precoces de la enfermedad vascular. Sin embargo, son necesarios más trabajos que confirmen esta relación. La confirmación de esta hipótesis abriría nuevas líneas no sólo en la fisiopatogenia de la fragilidad sino también en su manejo clínico ya que el ADMA (u otras formas de medir disfunción endotelial) podrían plantearse como un marcador precoz de fragilidad en pacientes sin enfermedad cardiovascular y ha sido propuesto por algunos autores como una diana fármaco-terapéutica[67].

Tal y como se comenta en la discusión, en su momento nos pareció que este trabajo tenía una importante limitación. Para establecer los niveles de fragilidad se utilizaron los Criterios del Fenotipo de Fragilidad (CFF) de Linda P. Fried[29], con los puntos de corte estandarizados a la población española. Inicialmente, con los puntos de corte originales, extraídos del Cardiovascular Health Study (CHS), observamos una gran prevalencia tanto de fragilidad como de prefragilidad que no parecían justificarse (respecto a prevalencias mostradas en la bibliografía) por diferencias socioeconómicas o sanitarias[29, 68]. Revisando la bibliografía encontramos que otros autores, sugerían que existen diferencias raciales significativas respecto a la composición corporal y, por lo tanto, a la cantidad de masa muscular y masa grasa, con la consiguiente repercusión en todas las medidas dependientes de la función física (por ejemplo velocidad de la marcha, fuerza de prensión y nivel de actividad física)[69]. En el caso concreto de los CCF se habían mostrado diferencias significativas en la prevalencia de fragilidad y prefragilidad en grupos raciales diferentes[70]. Estas diferencias dejaron de ser

significativas al aplicarse los criterios estandarizados a la población de estudio sugiriendo una disparidad racial[70]. Sin embargo, nadie había comparado la capacidad predictiva de los CFF originales con los CFF estandarizados a la población de estudio. Es decir, nadie había evaluado si el utilizar instrumentos no estandarizados a la población de estudio podría afectar a su validez.

6-. LA ESTANDARIZACIÓN DE LOS CRITERIOS CLÍNICOS DE FRAGILIDAD

El tercer objetivo de esta tesis fue comparar la prevalencia, tanto de fragilidad como de prefragilidad, utilizando los CFF con los puntos de corte originales de Linda P. Fried y los CFF con los puntos de corte estandarizados a la población española (S-CFF). Además, quisimos comparar ambos métodos diagnósticos en la predicción de hospitalización, muerte, discapacidad incidente y caídas. Este objetivo se desarrolla en el artículo titulado: "The standarization of frailty phenotype criteria improves its predictive ability. The Toledo study for healthy aging." (anexo IV de esta tesis)

Instrumentos utilizados. Operacionalización de los criterios de fragilidad

El Fenotipo de fragilidad fue operacionalizado de dos maneras (ver tabla 2):

- Criterios de Fenotipo de Fragilidad (CFF), utilizando los valores de corte estimados en CHS
- Criterios eStandarizados del Fenotipo de Fragilidad (S-CFF), utilizando la misma metodología que Fried y colaboradores utilizaron en el documento original. La velocidad de la marcha, la debilidad muscular y la actividad física se consideraron positivos si los valores se incluyen en el quintil más bajo de la distribución de la muestra del estudio.

La lentitud se definió mediante la prueba de velocidad de marcha sobre tres metros. A las personas se les pidió que caminaran 3 metros a su ritmo habitual dos veces. El mejor tiempo fue el elegido; Se utilizaron los puntos de tiempo ajustados por sexo y altura. La debilidad muscular se midió por la fuerza de agarre utilizando un dinamómetro hidráulico Jamar en la mano dominante. Después de tres repeticiones, el mejor resultado fue seleccionado y ajustado por el índice de masa corporal del sujeto. La pérdida de peso fue considerada positiva si existía una pérdida de más de 4,54 Kg no intencionada en el año anterior. La baja energía se

evaluó utilizando dos preguntas ("¿Cuántos días durante la semana pasada se ha sentido que todo lo que hizo fue un gran esfuerzo" y "¿Cuántas veces durante la semana pasada se ha sentido que no podía seguir haciendo cosas"). Las respuestas se puntuaron entre 0 y 4 dependiendo de la frecuencia de los síntomas; Si alguna pregunta fue contestada con una puntuación de 2 o superior, este criterio se consideró positivo. La actividad física se evaluó usando la Escala de Actividad Física para Personas Mayores (PASE) 28 en lugar del cuestionario de Tiempo Libre de Minnesota usado en CHS. El ajuste se ha hecho teniendo en cuenta la cantidad de calorías utilizadas para las actividades de ocio.

Tabla 2. Puntos de corte utilizados para definir los Criterios originales del Fenotipo de Fragilidad (CFF) y los Criterios Estandarizados a la población Española (S-CFF)

	CFF	S-CFF
Pérdida de peso	En el último año, ha perdido más de 10 libras (4.54 Kg) inintencionadamente? □ NO □ YES *Si la respuesta es si, este criterio es positivo.*	
Baja energía	Usando la escala de depresión CES-D, las siguientes dos preguntas deben realizarse preguntando cuantas veces en la última semana se han sentido de esta manera • Sentía que todo lo que hacía era un esfuerzo • No podía continuar 0=rara vez o nunca (< 1día) 2= moderada cantidad de tiempo (3-4 días) 1= alguna vez o poco tiempo (1-2 días) 3= la mayoría del tiempo *Si el sujeto contesta "2" o "3" a cualquiera de estas preguntas, este criterio es categorizado como positivo.*	

Lentitud	Velocidad de la marcha estratificado por género y altura	
	Hombres	*Hombres*
	Altura ≤173 cm……≤ 0.76 m/s.	Altura ≤164 cm……≤ 0.5m/s
	Altura >173 cm……≤ 0.65 m/s	Altura >164 cm……≤ 0.43 m/s
	Mujeres	*Mujeres*
	Altura ≤159 cm…… ≤ 0.76 m/s	Altura ≤152 cm……≤ 0.41m/s
	Altura >159 cm…… ≤ 0.65 m/s	Altura >152 cm……≤ 0.33m/s
	Si la velocidad de la marcha es más baja que estos puntos de corte, el criterio es positivo	
Debilidad muscular	Fuerza de prensión estratificada por género y los cuartiles del Índice de Masa Corporal (IMC):	
	Hombres	*Hombres*
	IMC ≤24…… ≤29 Kg	IMC ≤25.5…… ≤19.1 Kg
	IMC 24.1-26 …… ≤30 Kg	IMC 26.4-28 …….. ≤22.9 Kg
	IMC 26.1-28 …… ≤30 Kg	IMC 28.1-30.8 …… ≤22.9 Kg
	IMC >28 …….. ≤32 Kg	IMC >30.8 …….. ≤22.9 Kg
	Mujeres	*Mujeres*
	IMC ≤ 23 ……. ≤17 Kg	IMC ≤ 26.4 ……. ≤11 Kg
	IMC 23.1-26 ……≤17.3 Kg	IMC 26.5-29.5 ……≤12 Kg
	IMC 26.1-29 …… ≤18 Kg	IMC 29.6-32.9 …… ≤12 Kg
	IMC >29 …….. ≤21 Kg	IMC ≥33 …….. ≤12 Kg
	Si la fuerza de prensión es más baja que estos respectivos puntos de corte, el criterio es positivo	
Baja actividad física	Kcal de actividad física de ocio estratificada por género:	
	Hombres<383 Kcal (caminar al menos 2:30 horas a la semana).	*Hombres* <459.6 Kcal (caminar al menos 3 horas por semana)
	Mujeres <270 Kcal (caminar al menos dos horas por semana)	*Mujeres*<135 Kcal (caminar al menos 1 hora por semana).
	Si las Kcal de actividad física de ocio son más bajas que estos puntos de corte, el criterio es positivo.	

Resultados

Fueron incluidos en el análisis 1645 participantes. De ellos, 729 (44,38%) eran hombres y la mediana de edad era 74 años (IQR: 70-78). La prevalencia de fragilidad y prefragilidad utilizando los CFF fue de 24,12% y 66,4% respectivamente mientras que cuando se usó los S-CFF las prevalencias fueron 6,68% y 47,81%, respectivamente (p <0,01). Cuando observamos la clasificación de individuos dependiendo del instrumento, hubo diferencias en la clasificación según el instrumento utilizado en 880 personas (53.49%) (ver Tabla 3 del anexo IV). CFF mostró una clara tendencia a clasificar a los individuos en una condición de fragilidad más severa que la S-CFF. Entre los individuos clasificados como robustos según S-CFF, sólo el 20.23% (159/786) permaneció en la misma categoría que el CFF. En este mismo sentido, sólo un tercio de los individuos CFF frágiles (32,66%; 131/401) permanecieron en la misma categoría cuando se evaluaron utilizando S-CFF.

Durante el seguimiento, 244 sujetos (14,83%) fallecieron, 359 (21,8%) ingresaron en hospitales, 274 (16,65%) desarrollaron discapacidad incidente y 159 (9,66%) sufrieron al menos una caída durante el último año. Cuando se comparó la incidencia de estos eventos según el estado de fragilidad en función del instrumento utilizado, hubo diferencias estadísticas entre los individuos clasificados como prefrágiles en los eventos de muerte, hospitalización y discapacidad incidente y entre aquellos clasificados como frágiles en el evento de muerte. No se detectaron diferencias estadísticamente significativas en los individuos clasificados como robustos para cualquier resultado. En este mismo sentido, cuando se utilizan los S-CFF, la regresión logística (Tabla 5, anexo IV) riesgo mayor estadísticamente significativo de muerte, hospitalización y discapacidad incidente para los individuos prefrágiles y frágiles. Cuando se utilizaron los CFF ese riesgo fue

significativamente mayor solo para los frágiles. Ni CFF ni S-CFF encontraron diferencias significativas en el riesgo de caídas.

El tiempo en el que hacemos nuestra predicción es un factor importante cuando las personas mayores son el objetivo del pronóstico, ya que su expectativa de vida es limitada. Por eso evaluamos el tiempo necesario para que la diferencia entre las categorías alcance la significación estadística. Se crearon curvas de Kaplan-Meier no ajustadas para las variables en las que estaba disponible el momento del evento: muerte y hospitalización (Figura 1, anexo IV). Para ambas versiones de los criterios, el estado de fragilidad predijo la muerte y la hospitalización ($p < 0,01$). Además, se analizó el tiempo mínimo de seguimiento necesario para obtener diferencias estadísticamente significativas entre el robusto, prefrágil y frágil (Figura 2, anexo IV). Utilizando los S-CFF la predicción para muerte y hospitalización fue significativa en un menor espacio de tiempo tanto para individuos prefrágiles como frágiles.

Discusión:

Este trabajo muestra, por primera vez, que la estandarización de los CFF a las características de la población mejora su capacidad predictiva de dos maneras:

- Primero, identificando a los sujetos prefrágiles, de manera consistente, como un grupo intermedio de riesgo entre los individuos robustos y los frágiles.
- Segundo, haciendo significativas las diferencias de predicción, entre los distintos estadios de fragilidad, en un espacio de tiempo más corto. Esto es de radical importancia en sujetos con muy corta expectativa de vida.

Por lo tanto, la estandarización de los CFF a las características de la población mejora su validez como herramienta predictiva de base poblacional en sujetos de la comunidad. Sin embargo, los S-CFF pueden no ser útiles para poder conferir riesgos individuales de malos resultados a los pacientes que vemos cada día en la práctica clínica.

7-. ÁRBOLES DE DECISIÓN

Finalmente, el **objetivo 4** de esta tesis fue construir árboles de decisión para los eventos de muerte y discapacidad incidente a cinco años, un instrumento para la toma de decisiones de potencial utilidad en la práctica clínica diaria.

Resultados:

En el análisis se incluyeron 1646 sujetos con una edad media de 74 años (70.0-78.0), el 44.38% eran hombres. De todos ellos, 239 (14.52%) fallecieron a los 5 años. Teníamos datos de la evolución de la discapacidad a lo largo de esos 5 años de 1292 (78.49%) participantes. De ellos, 159 (12.3%) desarrollaron discapacidad incidente.

En la siguiente tabla resumimos las características basales de estos sujetos.

Variable	Todos (n=1646)	Vivos (n=1407)	Muertos (n=239)	No discapacidad incidente (n=1133)	Discapacidad Incidente (n=159)
Edad (años)	74.0 (70.0-78.0)	74.0 (70.0-77.0)	79.0 (75.0-83.0)***	73.0 (69.0-77.0)	79.0 (75.0-82.0) ***
Sexo (% hombres)	44.38	41.80	59.41***	43.43	33.12*
Altura (m)	1.57 (1.51-1.64)	1.57(1.51-1.64)	1.57 (1.51-1.65)	1.57 (1.52-1.65)	1.54 (1.48-1.60) ***
IMC (Kg/m2)	28.83 (26.06-31.99)	28.87 (26.22-32.02)	28.47 (24.93-31.64)**	28.83 (26.27-31.98)	29.05 (26.43-32.47)
Diabetes (%)	19.68	18.18	28.45***	17.49	26.11**
HTA (%)	50.55	45.60	51.39	50.8	49.04
ACV (%)	13.02	10.52	27.61***	10.56	12.739
ECV (%)	4.401	3.4	10.04***	3.28	6.36
EPOC (%)	8.37	7.65	12.5**	7.1	8.9
Cáncer (%)	5.86	5.72	6.69	4.4	5.5
Í. Charlson (%)			***		*
0	46.82	48.60	36.40	50.35	43.95
1	25.25	25.41	24.27	25.40	21.66
2	15.22	14.25	20.92	14.21	14.65
≥3	12.71	11.74	18.41	10.04	19.74
Polifarmacia (%)	32.09	30.42	41.84***	29.04	39.49**
Vm (m/s)	0.5 (0.42-0.73)	0.6 (0.42-0.75)	0.42 (0.33-0.6)***	0.6 (0.46-0.75)	0.43 (0.33-0.6)***

Discapacidad (%)			***		***
0	92.12	94.67	77.21	96.98	79.62
1	5.36	3.82	14.35	2.13	16.56
≥2	2.52	1.51	8.44	0.89	3.82
Caídas (%)	17.7	16.79	23.1**	15.96	24.19**
Estado cognitivo (%)			***		***
MEC					
≥24	57.05	58.33	48.65	61.23	33.33
19-23	33.14	33.66	29.73	32.22	48.41
≤18	9.81	8.01	21.62	6.55	18.26
Depresión(%)	18.03	16.85	25.12***	14.10	30.71 ***
S-CCF (%)			***		***
Robusto	45.51	48.89	24.27	52.75	25.48
Prefragil	47.81	46.39	57.32	44.41	59.23
Fragil	6.68	4.72	18.41	2.84	15.29

Los datos son medianas (percentil 25-75)

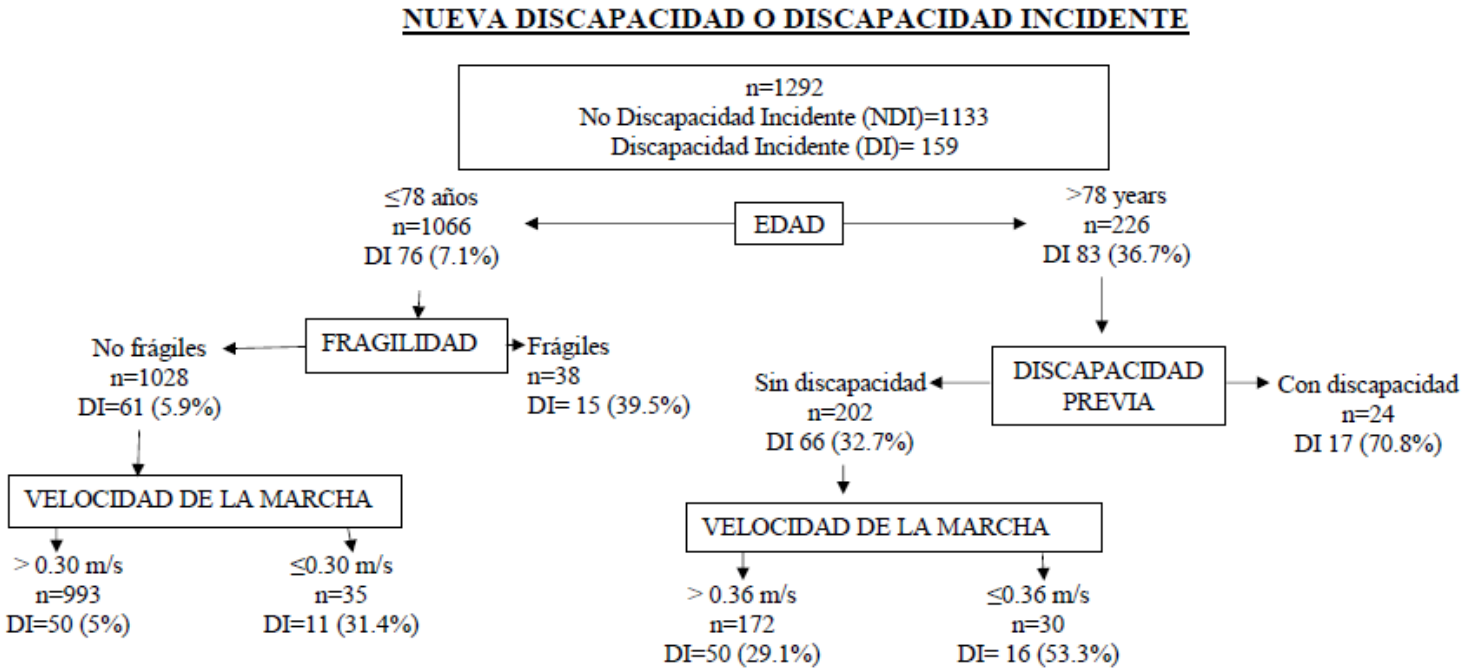
*: P-valor<0.05, **: P-valor<0.01, ***: P-valor<0.001 (Mann-Whitney)

Tabla 3-. Características basales de los sujetos incluidos en el análisis.

A la vista de los resultados previos, las variables estadísticamente diferentes que coinciden con lo extraído de la literatura previa, fueron introducidas en el análisis de particiones.

Tras realizar el análisis, el árbol de decisión para incidencia de nueva discapacidad a cinco años fue el siguiente:

Figura 7-. Árbol de decisión de discapacidad incidente a cinco años



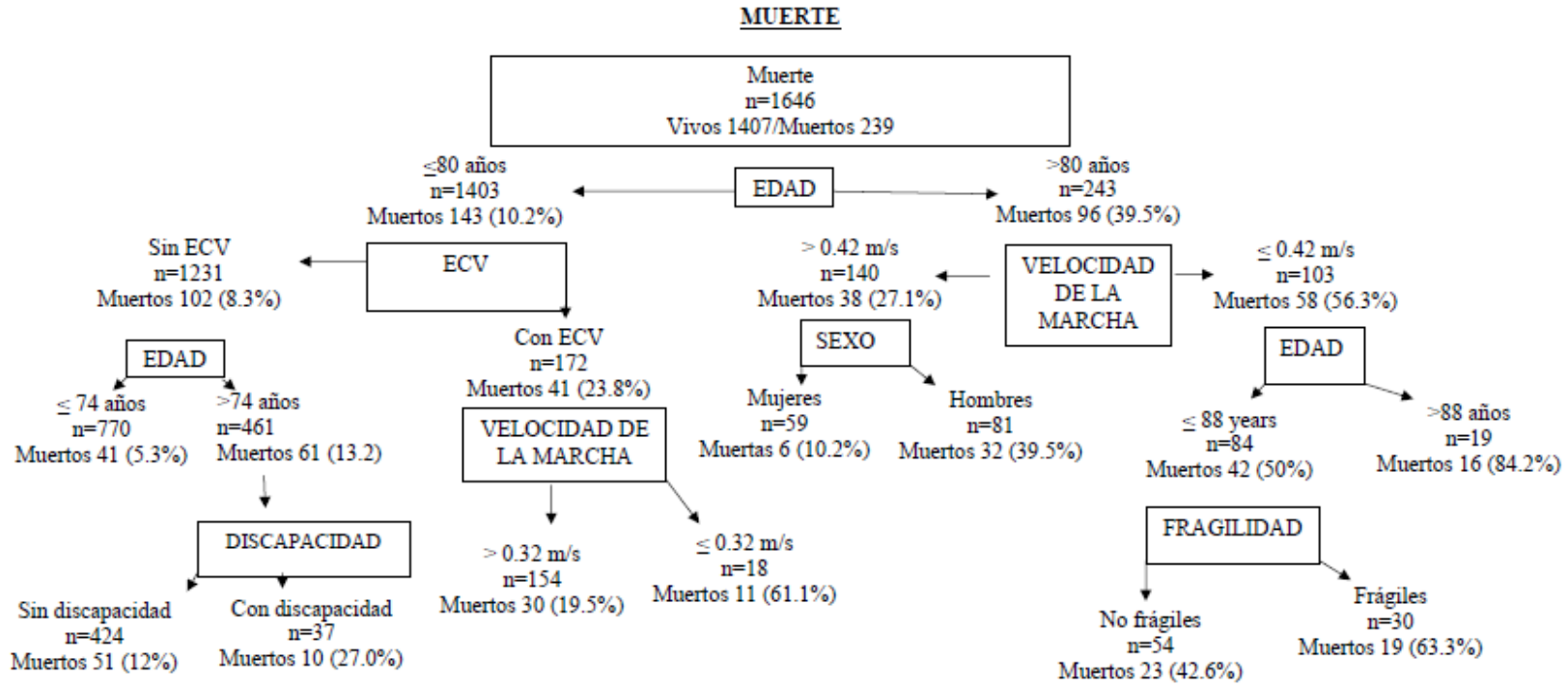
El modelo de regresión logística condicional del riesgo de subgrupos, representado por los nodos terminales en el árbol de decisión de la discapacidad incidente a cinco años es el siguiente:

	n	Riesgo de DI a 5 años	OR (LL-UL)	p
1-. ≤78 años, no frágil, vm≥0.3 m/s.	993	5.03%	1	1
2-. >78 años, sin discapacidad, vm≥0.36 m/s	172	29.1%	7.79 (5.04-12.04)	0.000
3-. ≤78 años, no frágil, vm<0.3 m/s.	35	31.4%	8.64 (4.00-18.64)	0.000
4-. ≤78 años, frágil.	38	39.5%	12.30 (6.05-25.02)	0.000
5-. >78 años, sin discapacidad, vm<0.36 m/s	30	53.3%	20.12 (9.41-43.00)	0.000
6-. >78 años, con discapacidad.	24	70.8%	45.8 (18.16-115.5)	0.000

Tabla 4-. Modelo de regresión logística condicional del riesgo de subgrupos de la discapacidad incidente.

Tras realizar el análisis, el árbol de decisión para mortalidad a cinco años fue el siguiente:

Figura 8-. Árbol de decisión de muerte a cinco años



El modelo de regresión logística condicional del riesgo de subgrupos, representado por los nodos terminales en el árbol de decisión de muerte a los cinco años es el siguiente:

	n	**Riesgo de MUERTE a 5 años**	**OR (LL-UL)**	**p**
1-. ≤74 años, sin enfermedad cardiovascular	770	5.3%	1	1
3-. >80 años, vm>0.42 m/s, mujer	59	10.2%	2.01 (0.82-4.95)	0.128
4-. 74-80 años, sin enfermedad CV, sin discapacidad	424	12%	2.43 (1.58-3.73)	0.000
4-. ≤80 años, con enfermedad CV, vm>0.32 m/s	154	19.5%	4.30 (2.58-7.14)	0.000
5-. 74-80 años, sin enfermedad CDV, con discapacidad.	37	27%	6.58 (2.99-14.52)	0.000
6-. >80 años, vm>0.42 m/s, hombre	81	39.5%	11.61 (6.73-20.03)	0.000
7-. 80-88 años, vm≤0.42m/s, no frágil.	54	42.6%	13.19 (7.06-24.63)	0.000
8-. ≤80 años, con enfermedad CV, vm≤0.32 m/s	18	61.1%	27.94 (10.29-75.84)	0.000
9-. 80-88 years, vm>0.42m/s, no frágil.	30	63.3%	30.71 (13.71-68.79)	0.000
10-. >88 años, vm ≤ 0.42m/s	19	84.2%	94.83 (25.56-338.56)	0.000

Tabla 5-. Modelo de regresión logística condicional del riesgo de subgrupos de la muerte

Discusión:

Estos árboles de decisión son unas herramientas de uso sencillo en la clínica diaria, que permiten conocer el riesgo individual de nueva discapacidad y muerte a cinco años. Asimismo, pueden servir para detectar subgrupos de pacientes sobre los que puede ser más beneficioso realizar una intervención. Es la primera vez que se presentan herramientas de este tipo, que permitan el acercamiento tan directo al paciente que acude a la consulta.

Existen varios subgrupos con muy alto riesgo, tanto de muerte como de DI. Sin embargo, cabe destacar que estos grupos son minoritarios. Sólo el 9.82% de los sujetos tiene un riesgo alto de discapacitarse (>30%) a los cinco años, mientras que el 76.85% de la población tiene riesgo bajo (5%). Ocurre lo mismo con la muerte: el 85.48% de las personas mayores de 65 años tiene un riesgo inferior al 20% de fallecer en los siguientes cinco años.

El análisis de particiones permite detectar las variables que mejor discriminan que el resultado final suceda o no suceda. La importancia de identificar estas variables radica en la posibilidad de que modificándolas (en el caso de ser modificables) en un determinado sujeto, varíe su riesgo de sufrir el resultado a estudio. Por ejemplo, en el árbol de decisión de la discapacidad incidente, las variables que resultaron discriminar mejor a los individuos que sufrían el evento han sido la edad, la velocidad de la marcha, la fragilidad y la presencia de discapacidad previa. La velocidad de la marcha y la fragilidad son variables modificables. En cambio, el árbol de predicción de mortalidad es diferente. Además de la edad, la velocidad de la marcha y la discapacidad, aparecen la enfermedad cardiovascular y el sexo. La mayoría de las variables que mejor discriminan el riesgo de mortalidad son variables no modificables lo que revela una mayor dificultad para modificar el riesgo de muerte a cinco años. Esto tiene mucho sentido a la vista de los resultados de múltiples trabajos observacionales: muestran un aumento progresivo y marcado de la expectativa de vida en los últimos años, cada vez más

cerca de la máxima duración de vida, lo que plantea un difícil objetivo terapéutico seguir aumentándola[3, 19].

En el árbol de decisión de discapacidad incidente, las variables que resultaron discriminar mejor han sido la edad, la velocidad de la marcha, la fragilidad y la presencia de discapacidad previa. Salvo la edad, todas ellas son variables de función. Concretamente, de función física. Es llamativo el resultado, especialmente teniendo en cuenta que en el modelo se habían introducido la comorbilidad, la polifarmacia, el deterioro cognitivo y la depresión. Esto nos lleva a plantearnos una de las principales críticas a los CFF: se centra especialmente en el sistema esquelético o lo que en la bibliografía algunos autores definen como "la fragilidad física", dejando de lado otras manifestaciones de la fragilidad[71]. Nuestros resultados muestran que las variables que mejor diferencian a los sujetos que van a sufrir discapacidad incidente son variables de función física, desterrando estas críticas. Por otro lado esto tiene sentido, ya que los CFF son criterios establecidos en base a la capacidad de predicción de las variables elegidas en el CHS[29] y porque cada vez existe más evidencia que muestra que la medidas físicas aisladas son excelentes marcadores de salud[72], predictores de efectos adversos[73] en los que la capacidad cognitiva está involucrada y juega un papel importante[74].

Revisando los resultados de ambos árboles, llama la atención que la primera variable que mejor diferencia los individuos a sufrir los diferentes resultados es la edad en ambos. En el árbol de la discapacidad incidente, el punto de corte es 78 años. En el árbol de la muerte, el punto de corte se sitúa a los 80 años. Esto sugiere la posibilidad de un cambio de comportamiento en ese tramo de edad. Sobre este aspecto deberíamos focalizarnos en el futuro.

Como conclusión, los árboles de decisión pueden ser herramientas clínicas de uso sencillo que permiten conocer el riesgo individual de nueva discapacidad y muerte a cinco años. Permiten

detectar subgrupos de pacientes sobre los que podría ser más beneficioso realizar una intervención.

8-. CONCLUSIONES

Las conclusiones de esta tesis son:

1-. La fragilidad es un proceso multidimensional con múltiples sistemas implicados en el que la composición corporal (cantidad de masa magra y masa grasa) juega un papel central. Hasta el momento, la evidencia es insuficiente para recomendar algún tratamiento farmacológico tanto para el manejo de fragilidad como de la sarcopenia.

2-. Existe una asociación entre la fragilidad y la disfunción endotelial, lo que refuerza la conocida relación entre la fragilidad y la enfermedad cardiovascular y apoya la hipótesis de un papel relevante del sistema vascular en el desarrollo de la fragilidad desde los estadios más precoces de la enfermedad.

3-. La estandarización de los Criterios del Fenotipo de Fragilidad a las características de una población concreta, aumenta su validez como herramienta diagnóstica de fragilidad, ya que mejora su capacidad predictiva de dos maneras:

- Identifica a los sujetos prefrágiles de manera consistente como un grupo intermedio de riesgo entre los individuos robustos y frágiles.
- Hace significativas las diferencias de predicción entre los distintos estadios de fragilidad en un espacio de tiempo más corto.

4-. Nuestros árboles de decisión pueden ser herramientas clínicas de uso sencillo que permiten conocer el riesgo individual de nueva discapacidad y muerte a cinco años, así como detectar subgrupos de pacientes sobre los que podría ser más beneficioso realizar una intervención.

9-. TABLAS Y FIGURAS

9.1. Índice de tablas

9.2. Índice de figuras

10-. BIBLIOGRAFIA

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11-. ANEXOS

11.1-. ANEXO I. ALCANCE DE LA TESIS

Con los resultados de esta tesis se han presentado los siguientes artículos:

- **Artículo 1**

Laosa O, Alonso Bouzon C, Castro M, Rodriguez Mañas L. Pharmaceutical interventions for frailty and sarcopenia. Current Pharmaceutical design. 2014;20(18):3068-82. PMID 24079768 Factor de Impacto 2015: 3.052.

- **Artículo 2**

Alonso-Bouzón C, Carcaillon L, García-García FJ, Amor-Andrés MS, El Assar M, Rodríguez-Mañas L. Association between endothelial dysfunction and frailty: the Toledo Study for Healthy Aging. Age (Dordr). 2014; 36(1):495-505. PMID 23959520 Factor de Impacto 2015: 2.500

- **Artículo 3**

Alonso Bouzón C, Carnicero JA, Gonzáles Turín J, García-García FJ, Esteban de la Torre A, Rodríguez-Mañas L. The standarization of frailty phenotype criteria improves its predictive ability. The Toledo study for healthy aging. JAMDA 2017, 2. pii: S1525-8610(16)30520-5. doi: 10.1016/j.jamda.2016.11.003. (Epub ahead of print). Factor de Impacto 2015: 6.616

Pharmaceutical Interventions for Frailty and Sarcopenia

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Abstract: Frailty has emerged as one of the most relevant clinical syndromes in older patients. This term relates to the loss of functional reserve that can occur in some older people following exposure to one or more low-intensity stressors placing them at high risk for developing a number of adverse outcomes such as disability, falls, hospitalization and death. Frailty is the outcome of two combined effects: the ageing process and other superimposed injuries like chronic disease or, indeed, psychological and social stressors. The mechanisms leading to frailty typically involve several systems: mainly hormones, oxidative stress, inflammation, immunity, and vascular system. One of the most outstanding pillars of the frailty syndrome is the loss of muscle quantity and function, referred to as sarcopenia. The main bulk of experimental pharmacological interventions addressing the clinical problem of frailty have been focused on the use of hormones, as replacement therapy in subjects with low or normal circulating basal levels of the hormone. Results have been disappointing, except for the case of testosterone that have shown some benefits. The effectiveness of other potential therapeutic interventions (antioxidants, anti-inflammatory agents, nutritional supplements) appears to be limited or has not been explored in detail until now. In conclusion, there is an available path to prevent the development of disability in older people through the treatment of frailty, its main risk factor. Aditional research and further experimental testing will help to identify new targets and help to make this journey successful.

Keywords: Frailty, concept, pathophysiology, pharmacological targets, treatment, RCTs.

INTRODUCTION

Distribution of mortality by age has changed in recent years. In the middle of the twentieth century mortality was concentrated between the sixth and eighth decade of life, but at the end of the twentieth century the distribution of mortality changed, becoming concentrated in the 9th and 10th decades [1]. In addition, the number of births who reach adulthood has increased exponentially which has decreased gradually the probability of dying at ages of 80 or 90 years [2]. As a consequence, the proportion of older people has increased, changing the shape of the population pyramid, which currently shows a narrow base and a growing vertex, and an increase in the number of centenarians especially in females from European countries and Japan.

This extraordinary change in life expectancy that occurred in the last century will not extend to the current century, as we are approaching maximum life expectancy, which is estimated to be around 110 years for humans, and a maximum life span for humans, which is around 120 years [3] Therefore, to prolong life is becoming a secondary aim and we should change our focus from living longer (a previous aim) towards living with a better quality of life. However, to tackle this challenge we must overcome several difficulties. The first one is that sometimes longevity brings disability, the main determinant of quality of life. In trying to embrace these facts in a unique concept, some authors have raised the concept of "successful aging" to describe the process of aging without disabilities or the process of aging in which disability is suffered only in the last months before death [4] Disability is considered to be the restriction or lack of ability to perform an activity according to individual characteristics. It can be caused by a disease (or a combination of several on the same subject) and is characterized by changes in the performance of a routine, in the execution of tasks, skills and behaviors and creates adjustment problems that limit individual functioning. It can be permanent or temporary, reversible or irreversible.

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Thus, improving or maintaining function becomes the supreme mission for medical care of older people. In addition, the best strategy is to prevent functional decline instead of trying to recover the function once this has been lost. This focus on prevention stems from two generalized observations: the reduced likelihood that functional independence in disability can be recovered [5] and the possibility to prevent incident disability by intervening in some conditions that predict the risk for disability [6]. This fresh approach to the issue of successful aging results in a new challenge in the management of the older patient. Modern geriatric medicine is changing its main focus from the recovery of lost function to the prevention of functional decline.

But, is disability an unavoidable consequence of aging or is it possible to diminish the prevalence of disability in older people? The answer to this question has been clearly answered in the last decade. One of the first studies showing a decrease in the percentage of older people with disability came from the United States [7]. In this latter study, the number of people older than 65 years with disability decreased around 25% between 1982 and 1999 (1.47%/year). Similar data has been shown in European studies in which a decrease of the prevalence of disability around 25% has been shown. This is the case in the Toledo Study of Healthy Aging, Spain. In this longitudinal, population-based study, the rates of dependency in Instrumental Activities of Daily Living decreased 22% in 15 years (1994-2009), which means a rate of 1.45% yearly. What is the forecast for future years? According to the 2012 European Ageing Report, the increase in life expectancy will continue, although at a lower rate than in the past century. Together with this fact, there is forecast a more important increase in Healthy Life Expectancy. For example, life expectancy at birth for a woman in 2008 was 80.8 years and it is estimated to be 89.9 years in 2060. At the same time, Healthy Life Expectancy for women in 2008 was 61.3 years and for 2060 is estimated to be 80.8 years. Therefore, healthy life years will increase more than life expectancy in the coming years [8], according to predictions made by the theory of the "compression of morbidity" some years ago. Thus, we now know that disability is avoidable, but we still need to establish the way that leads from robustness to disability, its influencing factors and its biomarkers.

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In addition to the necessity of putting the focus on function, a second relevant issue has emerged. Living better is not necessarily to live without disease, but to live without disability. Because of this, the role of disease in producing disability and the role of disability in the prognosis of the disease becomes of paramount importance and relevance. In particular, we need to take into account changes in the prevalence of the disease and their role in determining vital and functional prognosis. Moreover, the causes of mortality have changed significantly in the last years: from a dominance of communicable diseases at the beginning of the last century there has been a change in favor of the so-called non-communicable diseases, that is chronic diseases, mainly diabetes, cardiovascular diseases, respiratory disease and cancer [9]

At least until 2030, chronic diseases will maintain their leadership in determining not only death but disability [10]. However, it should be pointed out that the relationship between chronic diseases and disability involving its main risk factor, frailty, is conflicting. Few older patients with two or more chronic diseases are disabled and some older people without disease (or evidence of only mild disease) are frail. Indeed, functional status has been shown to be a better predictor of poor outcomes (including death) than chronic diseases in older patients, especially in those older than 80. This has been the case in the NHANES Study, where a functional marker is able to better predict adverse events such as hospitalization than chronic diseases [11]. More recently, a meta-analysis has shown that gait speed is the strongest predictor of the risk of dying in people older than 70 years at both five and ten years [12]. Finally, numerous studies have also shown that functional status is a good predictor of life expectancy and health costs until death [13].

In summary, the main aim at the present time is to enhance the health of older people by prolonging life expectancy free of disability. The ideal time for intervention is when disability has not yet occurred but people are still at risk. This stage between robustness and disability, where there is an increased vulnerability to develop adverse outcomes, has been called frailty [14].

The term frailty appeared in the literature in the 1980s. From the beginning it has been a concept difficult to define. Over the years the term has evolved, encompassing different aspects according to different authors: to be dependent or to be at risk of dependence, loss of physiological reserve, disengagement with the environment, chronicity of illness, medical and psychosocial problems, atypical presentation of the disease, and to be a potential target of geriatric care or experiencing accelerated aging, etc. Campbell and Buchner [15] considered frailty as a decline in reserve of multiple systems, which places the patient at risk for disability or at risk of death when subjected to a low-intensity stress. At the same time, other authors have attempted to investigate the pathophysiology of frailty. This is the case of Hamerman, who sought to clarify the relationship between clinical and biological mechanisms of frailty, arguing that frailty arises from an altered metabolic balance, manifested as an overexpression of cytokines and hormonal decline [16].

Although frailty and disability are tightly related, and they can coexist in the same individual, they are different entities. There are two key factors that differentiate frailty from disability. The first one regards the causes: disability arises from dysfunction of one system or multiple systems, while in frailty there is always a multisystem component. The second factor is that disability is not necessarily associated with "instability" (instability implying that small changes in the environment generate disproportionately large damage), a fact that is however intrinsic to frailty. These characteristics that clearly differentiate the two concepts in young older people (younger than 75-80 yrs. old) may be not easy to recognize at very advanced ages, when disability rarely responds to the involvement of a single system, and disability by itself increases both vulnerability and instability [17].

From what we have said until now we can draw four key ideas about the nature of frailty: frailty represents an state of increased vulnerability to lower stressors, it is different from disability, its manifestations are highly heterogeneous and, although associated with chronological age, its relationship is not linear.

One of the major challenges in the field of frailty has been the building of an operational concept of frailty. In view of the available data it can be said that frailty is a condition characterized by reduced physiological reserves, and that this creates a state of increased vulnerability in which the ability to respond to stress is limited [18] A second element of interest to the building of the concept of frailty is the role of disease in the development and / or worsening of frailty. When several diseases occur in the same subject, their impact on function is often not additive,, but a synergistic effect that multiplies the functional consequences of comorbidity. Trying to cope with these two characterstics, Fried´s group defined a clinical syndrome of frailty, characterized by the presence of at least three of the following five items: unexplained weight loss, fatigue, muscle weakness, slow gait and low physical activity (Table **1**) [18]. This clinical phenotype has demonstrated to have predictive value of several frequent adverse events in older people such as falls, urinary incontinence, dementia, functional dependence, atypical presentation of diseases, disorders of pharmacokinetics and pharmacodynamics, exacerbation of chronic disease, institutionalization and eventually death. This broad collection of events embraces to the majority of so-called geriatric syndromes, suggesting that these syndromes could be manifestations of extreme frailty, but representing only a small part of its full spectrum. As a consequence of this same point of view, geriatric medicine should cover the entire clinical spectrum that frail older people present with, and offer patients the opportunity for early detection and intervening at the early stages of frailty.

Strength (muscle weakness) is one of the most significant components of this phenotype. Many researchers have emphasized the functional correlation between frailty and deterioration in the performance of basic and instrumental activities of daily living. The loss of strength in lower limbs is the strongest independent predictor of institutionalization and disability, even in those patients with excellent function. This fact suggests that the musculoskeletal system is the main effector leading to frailty, although many systems and mechanisms are involved in producing it. For this reason, most models have proposed sarcopenia as a key element for the development of frailty. This whole process of muscle loss and decreased muscle strength, along with other changes in body composition, have functional consequences.

MECHANISMS OF FRAILTY

Physiological findings and other features that characterize frailty are not likely to be the result of changes in a single system, but rather due to the interaction of several systems resulting in a global process [19]. Mechanistically, frailty is a synergistic, multifactorial, complex phenomenon where sarcopenia is considered to be a major component in its pathway, but not the only one. In addition, the cycle of frailty classically described by Walston/Fried must be expanded as other components not initially considered to be related to frailty have shown evidence of such relationship in recent years [20, 21] (Fig. **1**). Thus, intrinsic changes in the skeletal muscle associated with the ageing process plus other factors contribute to frailty.

Skeletal Muscle Factors (Intrinsic Factors)

The age-related loss of lean body tissue (LBM) or muscle mass [22] associated with poor functioning [23-25] is known as sarcopenia. The process of sarcopenia begins at around the ages of 30-35 years, and reaches its major expression at very advanced ages. Depending upon the starting point (peak of muscle mass) and the rate

Table 1. Fried´s criteria for frail and pre-frail individuals.

1- **Weight loss**: Unintentional weight loss of 4,5 Kg during the last year
2- **Exhaustion**: Using the responses (YES/NO) to two statements of the CES-D Depression Scale
3- **Physical activity**: Assessed by the short version of the Minnesota Leisure Time physical Activity questionnaire
4- **Slowness**: Assessed by walk time and stratified by gender and height
5- **Weakness**: Assessed by grip strength and stratified by gender and Body Mass Index

Robust: None of the criteria; **Prefrail**: 1 or 2 criteria; **Frail**: ≥ 3 criteria

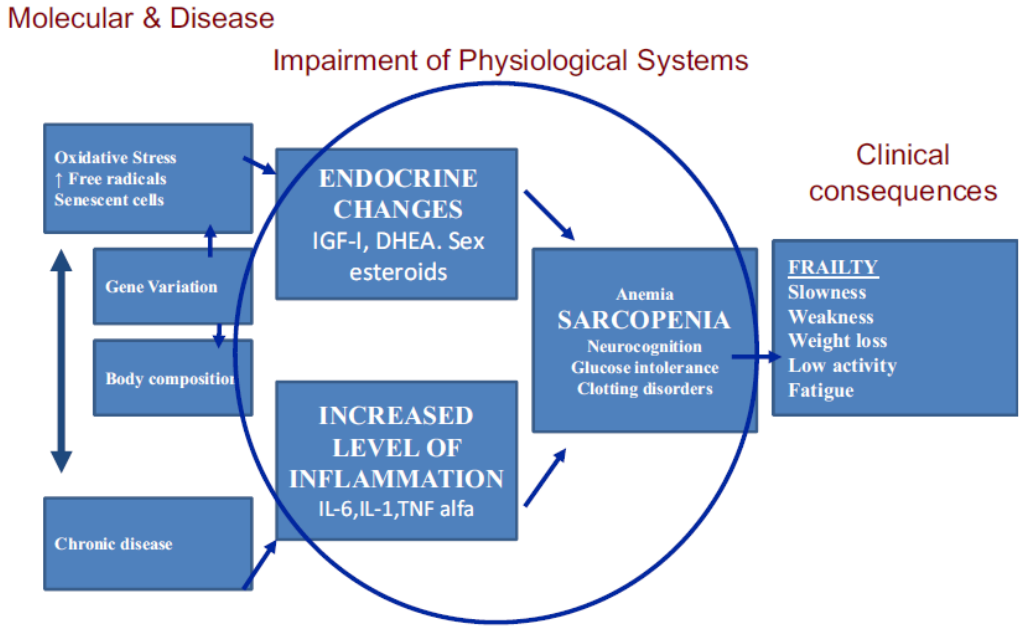

Fig. (1). Pathway of mechanisms underlying frailty. Sarcopenia is just one of its components. Adapted from Walston JM *et al*. [21].

of loss of muscle mass and function the pattern of clinical symptoms and consequences will develop.

The principal mechanisms underlying sarcopenia are:

1-. At a cellular level:

- Apoptosis is programmed cell death produced through controlled signaling pathways resulting in cellular self-destruction without any damage to the surrounding tissue [26]. Regulatory proteins, endonucleases, protease inhibitors and proteolytic enzymes, known as caspases, form a coordinated cascade that finishes with the cellular degradation and DNA fragmentation. Two major pathways of activation are distinguished based on the extrinsic or intrinsic origin of the stimulus [27]. Mitochondria is considered a key center for the induction and regulation of apoptosis [26]. During the aging process, an increased apoptosis has been shown in skeletal muscle. Myonuclear apoptosis could be a selective target for the development of preventive and therapeutic interventions on sarcopenia [27]. Behavioral interventions (caloric restriction, exercise training), several drugs and hormones (enalapril, acetaminophen, antimyostatin antibody) and genetic manipulations (PGC-1α overexpression) have shown to decrease apoptosis in the myocyte in animal (usually rodent) studies [27].
- Mitochondrial dysfunction and concomitant decreases in muscle mitochondrial ATP production are other mechanisms involved: many authors have shown a relationship of sarcopenia with alterations in mitochondrial DNA. Peroxisome proliferator-activated receptor-γ coactivador-1α (PGC-1α) is the major regulator of mitochondriogenesis. A lack of expression of PGC-1α in response to different stimuli (exercise training, cold induction or thyroid hormone treatment) in aging rats has been demonstrated pointing out the role of PGC-1α in the loss of mitochondriogenesis associated with aging. This transcriptional coactivator has also been proposed as a target for pharmacological interventions to prevent sarcopenia [28].
- A large evidence base supports the hypothesis that oxidative stress contributes to aging in many tissues, including muscle [29, 30]. The elevation in oxidative stress that occurs with aging can regulate redox-sensitive signaling pathways, increase catabolic gene expression and activate apoptotic pathways thereby contributing to the progression of sarcopenia [31]. One of the major sources of oxidant production is xanthine oxidase. Recently it has been shown that allopurinol (an inhibitor of xanthine oxidase) can increase maximal isometric force in the plantar flexor

muscles of aged mice after electrically stimulated isometric contractions [31].

2-. **A Tissue perspective:** in aged muscle, reduced neuronal stimulation is found based on three main changes: first, loss of motorneurons and concomitant remodeling of motor units through collateral reinnervation; second, impairment of neuromuscular activation and, lastly, uncoordinated patterns of intermuscular neural activation [32]. Additionally, molecular processes that occur during aging, described above, lead to a progressive shrinkage of the cross-sectional area of the muscular fiber, usually type II fibers [32]. The remaining type II fibers seems to maintain their efficiency probably by adjusting their capability to produce energy, as suggested by the absence of age-related changes in the enzymatic activities of the anaerobic machinery for energy production [30]. These structural changes contribute to poor muscle function and a decrease of strength and power.

3- Extrinsic factors: epidemiologic, physiological, pharmacologic and clinical studies have suggested other multiple contributing factors:

- Dysregulation of catabolic cytokines: the proinflammatory state of aging has been implicated in the development of sarcopenia due to the effect of increased cytokines on reduced muscle protein synthesis [33]. Particularly IL-6 and TNF-α that can act directly or through IGF-1 [34]. No relevant data about the locally generated cytokines (mainly through COX) are available.
- Loss of hormone production: With aging, anabolic hormone levels (sex hormones, GH, IGF-1) decrease, thus decreasing their effects on target organs/tissues. Testosterone affects muscle mass and muscle strength both directly and indirectly [33]. At muscular level IGF-1 stimulates protein synthesis and differentiation [33]
- Influence of external factors such as malnutrition, sedentary life-style and chronic diseases. Specific nutritional issues are related to functional impairments. This is the case for hypovitaminosis D, protein malnutrition, and abnormal glucose handling with insulin resistance (IR) [35]. Age-related IR is an independent determinant of poor muscle strength and function, increased myosteatosis, and increased catabolism [36].
- Exercise influences protein metabolism in skeletal muscle by changing oxidation rates of key amino acids, such as leucine, and increasing hypertrophy in the presence of adequate protein intake [35]. In particular, resistance training enhances the ability of aging muscle to retain fiber strength, decrease adipocyte infiltration, and increase metabolic function [37]. Inactivity greatly exacerbates catabolism and atrophy in skeletal muscle, with deficits in specific proteins (myosin and actin) involved in force producing an abnormal accumulation of collagen and fat [35].

Physiological functions that take place within muscle have a critical effect on the development of sarcopenia: muscles are the largest reservoir of body proteins and energy that can be used in periods of stress; aminoacids of the muscle can be mobilized during acute infections and are used for building antibodies; hormones are produced and catabolized in muscle tissue, it is the primary site of glucose availability playing a role when glucose metabolism is impaired and it is the major contributor to basal metabolic rate [33, 38]. All of these systems and mechanisms, that interact among them, contribute to keeping alive the physiopathologic cascade of sarcopenia once the process is underway [33].

Until now we have been reviewing the factors involved in producing, maintaining or aggravating sarcopenia. However, as we have previously stated, sarcopenia is not the sole mechanism in producing frailty, but one of several likely predisposing factors within the complex geriatric syndrome of frailty. This suggests that the frailty concept is more clinically oriented than the concept of sarcopenia, and corresponds more directly with the needs of clinicians for improved functionality and independence in a population who are at risk for developing disability and other adverse outcomes [33].

Along with sarcopenia, and interacting with it, the following factors must be taken into account:

Effects of Endocrine Changes

Hormonal changes with aging affects body composition and promotes declining muscle mass and strength seen in frail older adults [19].

In women, sex hormone levels decline fairly abruptly with the onset of menopause; in men, testosterone levels also decline, but more gradually. Testosterone decreases by 1% every year in men. The effect of this change is augmented by the concomitant decrease in sex hormone binding globulin which accompanies aging [39], raising the figure of those meeting the standard criteria for hypogonadism up to 50-80% in men over 80 years [40] . Although there are several cross-sectional and longitudinal studies that have reported an association between total and bioavailable levels of testosterone and measures of muscle strength and self reported and performance based measures of physical function [40, 41], others [42] have not found such a relationship. In this regard, Moir *et al* in a study of males, did not find an association between total and free testosterone levels and frailty phenotype, although a relationship with sex hormone binding globulin (SHBG) was seen. Recently, the association between testosterone levels and frailty was confirmed in men and women, in a large sample of Spanish community dwellers, showing a different behavior in men (inverse relation) and women (U-shaped relationship) [43]. This could have several implications for designing clinical trials for men and women.

In a recent study, estradiol was associated with the presence of frailty in postmenopausal women between 65 and 79 years old [44]. It must be understood that the relationship was direct; i.e. the higher the concentrations of estradiol, the higher the risk of frailty. In this latter study, high sensitivity C-reactive protein modulated the association suggesting an interaction between endocrine dysfunction and inflammation to produce frailty. The relationship of the endocrine and immune networks in aging and in the different domains that are characteristically associated with the frailty syndrome has already been analyzed by Paganelli *et al* [45].

Dehydroepiandosterone (DHEA) also declines, in men and women, with frailty [46]. These losses are associated with decrements in muscle mass, increased leptin levels, and depressed appetite and food intake [35].

Growth hormone levels also decrease with age. Compared with non-frail older adults, frail older adults have lower levels of insulin-like growth factor-1 (IGF-1), a messenger molecule stimulated by growth hormone, and being different components of the system GH/IGF-1 is an independent predictor of frailty [47]. Ghrelin is a neuropeptide that is produced by the stomach, stimulates feeding, and has reciprocity with GH and IGF-1. It is also decreased in frail older people [48]. Potential effect of exogenous Ghrelin should be the stimulation of GH and IGF-1 responsiveness while improving body composition and appetite. GH and IGF-1 are, by themselves, other potential targets for intervention in the development of frailty.

Three biological pathways could explain the association between low 25(OH)-vitamin D and frailty: bone, muscle and inflammation [49]. The positive effects of vitamin D on muscle are well established [50], but its relationship with frailty remains uncertain although several studies have already suggested an association [49, 51].

Effects of Inflammation

Activation of inflammatory and coagulation processes is known to increase with age but can also be independently associated with frailty. Markers for activation of these pathways include the interleukins (IL), C-reactive protein (CRP), Factor VIII, fibrin D dimer (FDD), and others [35]. With regards to the etiology of frailty, it has been hypothesized that inflammation maybe:

(a) a primary cause,

(b) a response to some insult or infection

(c) a surrogate for some other set of pathophysiological processes associated with dysregulation of cellular, nuclear, transcriptional, and other homeostatic controls [52].

Proinflammatory factors are injurious to muscle and are also thought to be central to sarcopenia since they decrease the rate of muscle repair and protein anabolism and increase catabolism through their inhibition of IGF-1, or in the case of TNF-α, directly triggering apoptosis [35]. Frailty is correlated with increased levels of white blood cells, particularly neutrophils, monocytes, and T-lymphocytes, such as CD8 and CD28, denoting abnormal immune response. Frailty is also associated with decreased levels of anti-inflammatory cytokines, such as IL-10 [53]. The dysregulation of immunity is mediated in part by IL-6, but may also be a function of a subclinical viral or bacterial infection [54]. In the Women's Health and Aging Studies, 87% were seropositive for cytomegalovirus infection, which, when coupled with high IL-6 levels, drastically increased the odds (20x) for frailty [54]. Infection and inflammation change protein kinetics. Stress results in an irreversible destruction of essential amino acids to provide substrates for gluconeogenesis. There is an increase in hepatic protein turnover, and alterations in blood coagulation systems, including FDD. Walston *et al* investigated the inflammatory response and biomarkers of thrombosis in the Cardiovascular Health Study showing for first time a relationship between inflammation and coagulation system in the development of frailty [55].

Cytokine production can also be heightened through genotypic anomalies, where a single nucleotide polymorphism (SNP) results in a ''pro-inflammatory genotype'' that may exaggerate responsiveness and explain why some people become frail while others do not under the effect of the same stressors [56]. Alterations in T cell–dependent immunity with aging, cumulative insults or infection is less well characterized. Analyses of antigen presenting cells (dendritic cells) that induce T cells showed that, in the presence of cytokines, maturation and antigenic presentation abilities are diminished in frail, aged persons, but not in healthy older adults [57]. In an investigation of the role of IL-6, monocytes, chemokine ligands, and stressors that up-regulate gene expression in frailty, it was found that frail persons have a two times greater expression of stress responsive genes that mediate inflammation through monocytes and cytokines. They also had a greater risk of overexpressing the chemokine ligand 10 (also known as interferon c inducible protein), which is a potent pro-inflammatory compound in robust persons, with a concomitant rise in IL-6 and monocyte stimulation [58].

Inflammation has also been shown in conjunction with subclinical normocytic anemia in frail older subjects, where hemoglobin and hematocrit are reduced. Increases in IL-6 are associated with abnormal hematopoiesis (by inhibiting production of erythropoietin or by interfering with normal iron metabolism) and chronic disease or infection in addition to muscle catabolism [59].

Hematological parameters and acute phase proteins, including high alpha-2 macroglobulin, fibrinogen and low albumin in addition to those previously cited, are also thought to predict frailty and its progression [34]. These alterations may be the result or the response to another pathophysiological set of processes related to oxidative stress, i.e. to the accumulations of insults from reactive oxygen species (ROS) [60].

Oxidative Stress

Oxidative stress is known to be causal factor for a number of pathological processes. There are several main systems proposed to be the sources for reactive oxygen speciaes (ROS): namely NADPH oxidase, xanthine oxidase, uncoupled NO synthase, and the mitochondrial respiratory chain [61]. ROS causes muscle damage, stimulates the apoptotic effects of TNF-a, and is thought to be central to the deficits of aging and sarcopenia [35]. Oxidative stress seems to be of relevance to regulate the adaptive responses to stress in skeletal muscle, including the development of hypertrophy after the appropriate stimulus of the fiber. This role is blunted in older animals [62].

Together with oxidative stress generated by the muscle cell, other potential sources of ROS generated by the microvasculature increase during aging. This oxidative stress is one of the origins for the microvascular endothelial dysfunction accompanying aging in people without cardiovascular disease or cardiovascular risk factors [61]. The presence of endothelial dysfunction could be involved in the diminished tissue capillary supply observed in aged muscle [63, 64] In this same regard, data from the Toledo Study of Healthy Ageing suggest a relationship between ADMA (an endogenous inhibitor of NO by competition with L-arginine, the natural substrate of NO-synthase) and frailty.

To combat oxidative stress several antioxidant systems exist. Antioxidant nutrients and defense mechanisms such as superoxide dismutase, glutathione peroxidase, or catalase systems must be robust to balance the adverse effects of oxidative stress. Each of these systems is dependent on several cofactors, including specific minerals like selenium, usually absent or scarcely present in the diet of older people. As a consequence, antioxidants and anti-oxidant enzyme systems are less capable in older people [65]. Frailty has been shown to be associated with high levels of oxidized glutathione (OR 1.8, CI1.2–2.5, $p<0.02$), and malonaldehyde (OR 2.8, CI1.6–4.7, $p<0.001$), both of them indicators of increased oxidative stress [66]. Smoking, which generates oxidative stress, has long been known to increase frailty, disability, and mortality [67].

Nutrition

Protein intake is of interest in frailty. It is thought that nitrogen retention is low and protein requirements are higher in frail persons. Due to changes in protein kinetics and increased turnover, there is evidence for an increased requirement of daily intake of proteins around 1.1–1.5 g/kg/d, together with some essential amino acids [68]. Muscle carnitine levels diminish with age, and carnitine is an amine central to skeletal muscle metabolism as well as to the production of energy for T-cells and deactivation of cytokines. Carnitine supplementation seems to improve myocyte atrophy and anorexia, both of them characteristic of frail people. Carnitine deficiency disrupts energy metabolism, endocrine control, and immunologic response. Carnitine is responsible for the transport of fatty acids across the mitochondria by means of carnitine palmitoyltransferase II (CPII), It appears that CP II deficiency may also play a role in age-related functional decline and frailty [69]. Alanine transferase, the protein responsible for conversion of alanine to alpha ketoglutarate, the first step in gluconeogenesis, is also decreased in frail persons and it is associated with a higher rates of mortality [70].

Landi *et al* [71] found that the serum levels of HDL cholesterol were inversely associated with mortality in community-living frail elderly over 80 years, supporting the hypothesis that HDL could be considered a valid biomarker for frailty.

Increases in B-type natriuretic peptide levels (protein responsible for decreasing blood volume) and elevations in the concentrations of glucose, sodium, and potassium in the blood have been correlated with frailty and its progression to disability and mortality. A composite index of plasma tonicity was modeled against

frailty and adjusted for sociodemographic, lifestyle, and other confounding variables. Hypertonicity increased the risk of frailty (OR 2.1, CI1.2–3.6, p<0.05), disability (OR 2.7, CI1.3–5.6, p<0.05), and mortality (OR 1.4, CI1.0–1.9, p<0.05) in a 10-year longitudinal study of people (N=561) older than 70 years [72].

Vitamin B_{12} and B_{12} transport proteins (transcobalamin I, II, III) and their genetic polymorphisms have been implicated in the pathophysiology of frailty in the Women`s Health and Aging Study [73, 74]. Cobalamine is a central methyl donor required for mitochondrial protein and nucleic acid synthesis through their active forms [28]. Some polymorphisms have been associated with an insufficient store of vitamin B12 that in turn activates the inflammatory pathway via mitochondrial dysfunction and increased oxidative stress with resulting DNA damage [74].

Caloric restriction has been shown to increase longevity. The response is thought to be mediated by a class of compounds called ''Sirtuins'' (SIRT) that are responsible for deacetylation and transfer with NAD and ADP [75]. When Sirtuins are activated, particularly SIRT1, metabolic responses are coordinated to heighten glucose tolerance, insulin sensitivity, mitochondrial adaptation, and fatty acid oxidation, which are decreased in aging and frailty [76].

It is thus evident that, many of the factors related to frailty are mechanistically difficult to separate from one another. Due to the inter-related nature of dysregulation that occurs on multiple molecular, cellular, and physiologic systems in frailty, an attempt to account for multidimensionality resulted in the term ''allostasis,'' which refers to an additive load of long-term stress that results in heightened pathophysiological responsiveness. In addition to ''allostasis'' in frailty, specific morbidities must also be considered. In a cross sectional analysis in the Cardiovascular Health Study the disease burden, measured by characterizing vasculature, brain, kidneys, lungs and glucose metabolism, was independently associated with frailty reinforcing its relationship with comorbidity [77].

PHARMACEUTICAL INTERVENTIONS

Despite the individual (loss of quality of life) and social (economic burden on healthcare systems) concerns associated with the frailty syndrome, few clinical trials (CT) have focused on frailty specifically. Moreover, the results are scarce and disappointing. Probably one of the most important limitations of research in this area is the lack of an agreed standardized global clinical definition of the frailty syndrome [78]. This may be a reason why sarcopenia is used as a surrogate outcome of frailty. Although sarcopenia is also a controversial concept, some of its components can be easily measured and the effects of the interventions on these measurements appropriately evaluated.

In this review, we will examine the clinical evidence published on pharmacological treatment of frailty and/or sarcopenia, focusing on the clinical trials with different drugs.

Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)

A multiplicity of clinical trials have evaluated the effects of ACE inhibitors on cardiac muscle in people with different diseases and ages. However, the effect of this family of drugs on skeletal muscle is still rather unclear.

Results from the Women´s Health and Aging Study showed for the first time data suggesting that ACE inhibitors could have additional effects to those demonstrated on cardiovascular system. This longitudinal study, aimed to study the role of different factors in the progression of disability/functional impairment, evaluate whether ACE inhibitors also prevent reduction in physical performance and in muscle strength in older hypertensive women who do not have heart failure. In this observational study, the participants who had taken ACE inhibitors continuously showed a lower mean decline in muscle strength of -1.0 kg (SE 1.1) 3-years after baseline evaluation compared with -3.7 (SE 0.5) kg in continuous/intermittent users of other antihypertensive drugs (p=0.016) and with -3.9 kg in those who had never used antihypertensives (p=0.026). Therefore, ACE inhibitor treatment seems to slow the decline in muscle strength in elderly women with hypertension and without heart failure [79].

More recently, another observational study (Women Health Initiative Observational Study) carried out in more that 27,000 women 65-79 years old at baseline, did not find any association between taking ACEs and incident frailty (measured by Fried´s criteria) after three years of follow-up [80]. Other observational studies have yielded conflicting results.

One randomised clinical trial (RCT) was carried out to assess the effect of perindopril over 20 weeks compared with placebo on the change in the 6-minute walking distance. It was a double-blind RCT, and participants were 65 years old and older who had problems with mobility or functional impairment. A total of 130 participants were enrolled in the study (mean age 78.7, SD 7.7 years) and 95 completed the trial. The results showed that the mean 6-minute walking distance was significantly improved in the perindopril group relative to the placebo group (mean between-group difference 31.4 m, 95% confidence interval [CI] 10.8 to 51.9 m; p = 0.003). Moreover, there was a significant impact on health-related quality of life.

Therefore, perindopril was found not only to improve physical function, as reflected by an increase in exercise capacity, but also to prevent deterioration in health-related quality of life in functionally impaired elderly people [81]. The explanation for this potential effect of the inhibition of ACE system is far from clear. In addition to the potential effect on the RAS system (in the microvessels of the musculature), there is evidence of local generation of angiotensin II by the skeletal muscle. These facts, together with the promising results of the previously cited studies, should promote the design and development of new clinical trials to clearly establish the effectiveness of these treatments.

Vitamin D

In recent years an association between vitamin D deficiency and frailty has been established. It is well known that vitamin D may improve muscle strength through a mechanism involving a highly specific nuclear receptor in muscle tissue and that this is linked with the reduction in the incidence of fractures in older adults probably mediated by effects of vitamin D on neuromuscular function. Vitamin D deficiency is common among older people and can cause mineralization defects, bone loss, and muscle weakness. Both observational and interventional studies have yielded evidence on the benefits of vitamin D on muscle performance and physical function. An epidemiological study done in an ambulatory US population composed of 4100 subjects older than 60 years established the association between low 25-hydroxyvitamin D levels and function in the low extremities. The results showed that 25-OHD serum concentrations between 40 and 94 nmol/L were associated with better musculoskeletal function in the lower extremities than concentrations $\leq$ 40 nmol/L [82].

Some studies have assessed the benefits of the supplementation of vitamin D in elderly people with low vitamin D levels. A randomised, double-blind and placebo-controlled clinical trial was designed to determine the effects of vitamin D supplementation on aspects of neuromuscular function (a well-established risk factor for falls and fractures). One hundred and thirty nine ambulatory subjects ($\geq$ 65 years) with a history of falls and low levels of 25-hydroxyvitamin D (25-OHD) were enrolled in the study. The results showed that vitamin D supplementation, in fallers with low levels of vitamin D, has a significant beneficial effect on functional performance, reaction time and balance, but not on muscle strength [83].

Later studies have shown that the benefits are not restricted to older people with low 25-OHD levels, spreading this benefit to

other groups of older patients. These clinical trials have been done in in-patients and out-patients, men and women, younger and older than 75 years old. These results support the recommendation of using vitamin D supplements in patients at risk for falls, with or without low plasma levels of 25-hydroxyvitamin D [84].

However, these clinical trials have been focused in decreasing the risk of falls by means of improving balance, sway or neuromuscular function, but not decreasing incident sarcopenia or frailty or their evolution to disability. So, data from further clinical trials are necessary to endorse the use of vitamin D supplements in frailty and sarcopenia.

Hormones

TESTOSTERONE

The effect of testosterone of increasing muscle mass and strength in young individual is well known, but the effect in older people is less clear. The results of different studies are not conclusive as to recommend the widespread use of testosterone in these patients.

It is well established that in subjects over 65 years the serum testosterone levels tend to be reduced considerably, a state that has become known as andropause. Free testosterone levels begin to decline at a rate of 1% per year after age 40 years [39, 85, 86]. It is estimated that 20% of men aged 60-80 years have levels below the lower limit of normality in adult men [87]. This decrease has been directly associated with an increased risk of falls, muscle weakness and frailty in older people [44]. It therefore appears that testosterone treatment in older men would be clearly justified from a physiological viewpoint. In women, although low testosterone levels seem to be also related to frailty [43], treating older women with testosterone raises a set of additional concerns. In women the most important issue from a hormonal point of view is menopause that also causes a sudden drop in sex steroid hormones, which leads to loss of bone density but also to muscle weakness. Moreover, recent studies [43] suggest that the relationship between frailty and estrogens could be opposite to the one expected: frailty seems to be associated with high estrogen levels in older (i.e. postmenopausal) women.

Results of clinical trials carried out with testosterone supplementation in different ages and with several clinical conditions are varied and conclusions about its use warrant careful consideration.

In young people, studies carried out with testosterone supplementation in men aged 19-68 years with hypogonadism have shown an increase in strength and muscle mass. Replacement doses of testosterone of 100 mg/day IM during 10 weeks increased fat-free mass and muscle size and strength in seven hypogonadal men 21-47 years old [88] Similar results have been showed by Wang *et al* in a CT in 67 hypogonadal men that received 5mg of sublingual testosterone (SLT) three times daily. The results show that total body ($P = 0.0104$) and lean body mass ($P = 0.007$) increases with SLT treatment in the 34 subjects in whom body composition was assessed. Leg muscle strength, assessed by leg press, was increased significantly over the 6 months of supplementation [89].

In a study carried out in young people with VIH results show that testosterone supplementation increases muscle bulk but does not improve strength and fatigability. Only exercise was able to increase muscle power and strength [90].

In contrast with these results, studies conducted in older people have conflicting results. The doses used in older people in these studies are lower that those used in young people due to the higher frequency of adverse events [85]. This is one of the potential explanations of the lower success of testosterone supplementation in older people.

In general, studies with testosterone supplementation in older people have shown an increase in fat-free muscle mass, but not an increase in the strength.

Snyder *et al* carried out a trial in 108 men 65 years and older with plasma levels of testosterone below normal. They were randomized to a testosterone patch (6 mg/daily) or placebo during 36 months. The results observed were a significantly different increase in lean mass in the testosterone-treated men principally in the trunk, but no significantly difference between the two groups regarding changes in strength, measured by means of knee extension [91]. Wittert *et al* obtained similar results in a randomized controlled trial carried out in 76 healthy men who were 60-86 years old and with borderline testosterone levels. The treatment consisted of 80 mg/twice daily of oral testosterone or placebo during 12 months. Results showed an increase in lean body mass and a decrease in fat mass but without effects on the muscle strength [92].

Sih *et al* published a RCT placebo-controlled in 32 hypogonadal men with a mean age of 68 ± 6 yrs.. They were randomized to treatment with placebo or with 200 mg of testosterone cyprionate biweekly for 12 months. The results showed that testosterone group tended to improve bilateral grip strength but without reaching statistical significance [93].

Kenny *et al* published an RCT in sixty-seven men (mean age 76 ± 4 years) with bioavailable testosterone levels below 4.44 nmol/l (lower limit for adult normal range). All patients in both groups were treated with calcium and vitamin D supplements. Results demonstrated that testosterone supplements prevented the lack of bone but is not better than placebo for improving muscle strength. Both groups showed similar results over muscle strength, probably due to the effect of vitamin D [94].

More recently, this same group published the results of a study in one hundred and thirty-one men (mean age 77.1 ± 7.6) with low plasma testosterone levels, a history of fracture, or low bone mineral density and frailty. This study showed similar results than their previous publication, confirming that supplementation with testosterone increased testosterone levels and had favourable changes in body composition, modest changes in axial bone mineral density, but didn´t have substantial changes in physical function [95].

In contrast with these results, Page *et al* published an RCT in seventy men with low serum testosterone (<350 ng/dl), 65 years and older and randomized to one of three regimens for 36 months: 1) Testosterone enanthate, 200 mg im every 2 wk, with placebo pills daily (T-only); 2) Testosterone enanthate, 200 mg every 2 wk, plus 5 mg Finasteride daily (T + F); or 3) placebo injections and pills (placebo). The results showed that T therapy (with or without Fiansteride) significantly improved performance in a timed functional test when compared with baseline and placebo and increased handgrip strength compared with baseline and placebo ($P < 0.05$). T therapy also increased lean body mass and decreased fat mass [96].

Similar results have been reported by Srinvas-Shankar *et al* in a randomized placebo controlled RCT carried out in 274 pre-frail and frail older men with testosterone levels below normal and treated with transdermal testosterone 50 mg/daily or placebo gel for 6 months. They demonstrated that physical function improved in testosterone group [97].

In addition to those results about the effect of testosterone on functional variables, it seems clear that testosterone supplementation in older people with low plasma levels or at the lower limits of normal, also can preserve muscle thickness. Atkinson *et al.* reported a randomized, placebo-controlled study in 30 pre-frail or frail patients with ages between 60-89 years, who were randomized to receive 50 mg of transdermal testosterone or placebo for 6 months, proving that treatment with testosterone preserved muscle thickness [98].

The limitation is that these effects on muscle strength, lean mass and QoL are not maintained over the time as shown by O´Conell *et al* in 274 intermediate-frail and frail elderly men with low testosterone levels [99].

A summary of the most relevant of these studies is shown in Table **II**.

Dehydroepiandrosterone (DHEA)

DHEA is a steroid precursor of testosterone. DHEA and its sulfated form DHEA-S are produced by the adrenal cortex and the biological role of these hormones is not yet well defined. Observational cohort studies have demonstrated that plasma levels of DHEA and its sulfated form decline by 80% between the ages of 25 and 75 years and this decrease is greater after 80 years. In parallel, muscle mass and strength also decline with age.

Published data about DHEA replacement in older people are confusing and conflicting. In fact, there are few studies of DHEA supplements and evaluation of muscle function. Moreover, most of them are made with small populations with an age between 50 and 70 years, making the extrapolation of the results to the general population of older people a major issue.

The mechanism by which DHEA improves muscle function is unknown but it seems that administration of a 50 mg daily dose of DHEA for 3 months to men and women 40-70 years of age results in an elevation (10%) of serum levels of insulin-like growth factor-I (IGF-I) accompanied by improvement in self-reported physical and psychological well-being [100]. In this first study, the DHEA replacement was well tolerated. The same authors designed a double-blind placebo-controlled cross-over trial in healthy non-obese middle-age (50-65 yrs of age) men (n = 9) and women (n = 10) who were treated with 100 mg/daily supplementation of DHEA for 6 months and placebo for other 6 months. The results showed reduced body fat mass and increased muscle strength at the knee and lumbar back. These results were more evident for men than for women probably due to a gender differences and/or the presence of confounding factors in women (e.g. estrogen replacement therapy) [101].

Different randomized studies published more recently have not demonstrated any benefits of supplements with DHEA in older population and thus it cannot be a general recommendation for this population.

Percheron *et al* published (2006) the results of a randomized placebo controlled trial in 280 ambulatory and independent men and women between 60 and 80 years. They were randomized to a 50 mg/daily dose of DHEA or placebo for 6 months. The results observed didn´t show positive effects for building muscle mass or losing fat mass attributable to a DHEA supplementation [102].

Similar results were published by Nair *et al* who carried out a randomized controlled placebo trial comparing treatment with testosterone (5 mg/daily patch), DHEA (75mg/daily tablet) and placebo in elderly men and women; they found no beneficial effects of DHEA nor low-dose testosterone on body composition, physical performance, insulin sensitivity, or quality of life [103].

Other clinical trials support the hypothesis that treatment with DHEA supplements does not improve the frailty syndrome or prevent its development [104, 105].

In contrast, some studies support the idea that DHEA supplementation improves lower extremity strength and function in older frail women when combined with an aerobic exercise program. The physical function findings are promising and require further evaluation as frail women who are at high risk for falls and fracture. Table **III** summarizes the clinical trials done with DHEA.

Growth Hormone (GH)

In healthy adults, growth hormone (GH) secretion declines with increasing age. GH is required during childhood and adolescence to assure normal growth as well during adulthood to maintain bone and muscle strength [86]. GH stimulates the liver and other organs to produce insulin like growth factor 1 (IGF-1). Skeletal muscle is responsible of a quarter of the total production. There are two isoforms of IGF-1 and skeletal muscle is responsible of producing one of them. Exercise regulates the IGF-1 production [85]. Although GH supplementation might be expected to increase muscle mass and strength, the benefits of therapy found in clinical trials are not clear and the level of recommendations are not defined [86].

It has been observed that treatment with GH supplementation during 12 months in patients aged 60-79 years with GH deficiency (GHD) doesn´t cause significant changes on structural and functional cardiac parameters and increases maximal working capacity transiently [106].

Furthermore, GH supplementation in patients between 60-77 years with GHD may be accompanied by improvement in certain measures of cognitive function, but not in frailty or sarcopenia [107].

In a prospective open-labelled study, the effects of 10 years of GH replacement on muscle strength and neuromuscular function were followed in 24 older GHD patients (mean age of 65.2 years; range 61-74 years) showing that replacement therapy leads to a transient increase in isometric knee flexor strength, and provides protection from most of normal age-related decline in muscle performance and neuromuscular function [108].

However, further prospective studies are required measuring these same outcomes in older patients before making a general recommendation for the use of these treatments not only in GHD patients but also.in healthy older people.

The rate of synthesis of myofibrillar proteins is slower in muscle of healthy subjects over 60 yr old than in young adults. In a controlled clinical trial carried out by Welle *et al* (published in 1996) it was shown that GH supplements can increase muscle mass and strength in healthy men over 60 yr old, but does not restore a youthful rate of myofibrillar protein synthesis. This clinical trial, however, provides a major difficulty in the extrapolation of the findings since there were few patients and the average age was below 80y [89].

Papadakis *et al* conducted a RCT in 52 healthy men older than 69 (range, 70 to 85 years) with well-preserved functional ability but low baseline levels of insulin-like growth factor 1. Participants were randomized to growth hormone (0.03 mg/kg of body weight) or placebo given three times a week for 6 months. The results obtained showed that lean tissue mass increased and fat mass decreased significantly in the GH replacement group but this did not lead to an improve in the functional status. Additionally, the side effects were more frequent in GH replacement group than in the placebo group [109].

It is important to note that the use of GH in older people is associated with some adverse events. In the majority of the published studies side effects were significantly higher in the GH group compared with placebo. There are some differences in side effects between younger and older people following treatment with GH. In younger patients, the most important side effects are related to fluid retention while in older patients they are hyperglycemia, gynecomastia, fluid retention, arthralgia and carpal tunnel syndrome.

Table **IV** summarizes the most outstanding characteristics of these trials. From their results, the recommendation is that the use of GH in older people without GH deficiency cannot be recommended in clinical practice.

Table 2. Summary of Research Clinical Trials using testosterone to treat frailty or sarcopenia.

Article	Design	N	Treatment	Results
Atkinson *et al* [98]	Randomized and placebo controlled	30 (prefrail and frail) 60-89 years Low or borderline testosterone levels	Transdermal testosterone (50 mg) or placebo gel daily for 6 months	Testosterone treatment resulted in a preservation of muscle thickness at 6 months while it decreased in the placebo group (effect size 1.4 [95% confidence interval=0.3-2.5; p=0.015]
Wittert *et al* [92]	Randomized and placebo controlled	76 healthy men (60-86 years) Borderline testosterone levels	Oral testosterone 80 mg twice daily 12 months or placebo	Lean body mass increased (p =.0001) and fat mass decreased (p =.02) in the testosterone as compared with the placebo-treated group. There were no significant effects on muscle strength.
Wang *et al* [54]	Randomized and placebo controlled	67 hypogonadal men	Sublingual testosterone (T) cyclodextrin (SLT; 5 mg, three times daily	Total body (P=0.0104) and lean body mass (P=0.007) increased with sublingual testosterone treatment in the 34 subjects in whom body composition was assessed. Increased leg muscle strength, assessed by leg press (0 months, 139.0 +/- 4.0 kg; 6 months, 147.7 +/- 4.2 kg; P=0.0038)
Snyder *et al* [91]	Randomized and placebo controlled	108 men 65 years or older. 1SD below normal testosterone level	Testosterone patch or a placebo patch. 36 months Patch delivers 6 mg/day.	Lean mass increased (1.9+/-0.3 kg) in the testosterone-treated men, which was significantly different (P < 0.001) from that (0.2+/-0.2 kg) in the placebo-treated men. The decrease in fat mass in the testosterone-treated men was principally in the arms (-0.7+/-0.1 kg; P < 0.001 compared to the placebo group) and legs (-1.1+/-0.2 kg; P < 0.001), and the increase in lean mass was principally in the trunk (1.9+/-0.3 kg; P < 0.001). Change in strength of knee extension and flexion at 60 degrees and 180 degrees angular velocity during treatment, however, was not significantly different between the two groups.
Srinivas-Shankar *et al* [97]	Randomized and placebo controlled	274 men prefrail and frail, 65 years or older, testosterone level below normal	Transdermal T (50 mg/d) or placebo gel for 6 months	Isometric knee extension peak torque improved in the T group (vs. placebo at 6 months), adjusted difference was 8.6 (95% confidence interval, 1.3-16.0; P = 0.02) Newton-meters. Lean body mass increased and fat mass decreased significantly in the T group by 1.08 +/- 1.8 and 0.9 +/- 1.6 kg, respectively. Physical function improved among the oldest and frailest men.
O´Conell *et al* [99]	Randomized and placebo controlled	274 intermediate-frail and frail elderly men aged 65-90 years with low T levels.	Testosterone gel (25–75 mg/d) or placebo for 6 months	The effects of 6-month T treatment on muscle strength, lean mass, and QoL in frail men are not maintained at 6 months post treatment.
Kenny *et al* [94]	Randomized and placebo controlled	Sixty-seven men (mean age 76 +/- 4 years, range 65-87) with bioavailable testosterone levels below 4.44 nmol/l (lower limit for adult normal range)	Transdermal testosterone (two 2.5-mg patches per day) or placebo patches for 1 year. Plus 500 mg supplemental calcium and 400 IU vitamin D.	Testosterone group had a 0.3% gain in femoral neck BMD, whereas the control group lost 1.6% over 12 months (p =.015). Improvements in muscle strength were seen in both groups at 12 months compared with baseline scores. Strength increased 38% (p =.017) in the testosterone group and 27% in the control group (p =.06), with no statistical difference between the groups. Transdermal testosterone (5 mg/d) prevented bone loss at the femoral neck, decreased body fat, and increased lean body mass in a group of healthy men over age 65 with low bioavailable testosterone levels. In addition, both testosterone and placebo groups demonstrated gains in lower extremity muscle strength, possibly due to the beneficial effects of vitamin D.
Kenny *et al* [95]	Randomized and placebo controlled	131 men (age 77.1 +/- 7.6) with: -low testosterone levels -previous fracture, or -low bone mineral density -frailty	Testosterone 5 mg/d or placebo for 12 to 24 months; Calcium (1500 mg/d diet and supplement) Cholecalciferol (1,000 IU/d).	Increased testosterone levels in the treatment group. BMD on testosterone group increased significantly at the femoral neck and the lumbar spine (P=.005) and decreased at the mid-radius. There was an increase in lean mass and a decrease in fat mass in the testosterone group. No differences in strength or physical performance between groups were observed.

(Table 2) Contd....

Article	Design	N	Treatment	Results
Page *et al* [96]	Randomized and placebo controlled	70 Seventy men with low serum T (<350 ng/dl), age 65 yr and older (70+4)	Three regimens for 36 months: 1) T enanthate, 200 mg every 2 wk, with placebo pills daily (T-only); 2) T enanthate, 200 mg every 2 wk, with 5 mg F daily (T + F); or 3) placebo injections and pills (placebo).	T therapy significantly improved performance in a timed functional test when compared with baseline and placebo [4.3 +/- 1.6% (mean +/- sem, T-only) and 3.8 +/- 1.0% (T + F) vs. -5.6 +/- 1.9% for placebo ($P < 0.002$ for both T and T + F vs. placebo)] and increased handgrip strength compared with baseline and placebo ($P < 0.05$). T therapy increased lean body mass [3.77 +/- 0.55 kg (T-only) and 3.64 +/- 0.56 kg (T + F) vs. -0.21 +/- 0.55 kg for placebo ($P < 0.0001$)], decreased fat mass.
Sih *et al* [93]	Randomized and placebo controlled	15 hypogonadal men (mean age 68 +/- 6 yr) assigned to placebo, and 17 hypogonadal men (mean age 65 +/- 7 yr) assigned to testosterone.	Men received injections of placebo or 200 mg testosterone cypionate biweekly for 12 months	Testosterone improved bilateral grip strength ($P < 0.05$ by ANOVA) and increased hemoglobin ($P < 0.001$ by ANOVA). Testosterone supplementation improved strength, increased hemoglobin, and lowered leptin levels in older hypogonadal men. Testosterone may have a role in the treatment of frailty in males with hypogonadism; however, older men receiving testosterone must be carefully monitored because of its potential risks.

Table 3. Summary of Research Clinical Trials using Dehydroepiandrosterone (DHEA) to treat frailty or sarcopenia.

Article	Design	N	Treatment	Results
Morales *et al* [100]	Randomized placebo controlled cross-over	13 men /17 women, 40-70 yrs	DHEA administration (50 mg) for 6 months	DHEA supplementation to young adults increase levels of in IGF-I, improve physical and psychological well-being in both genders with absence of side-effects.
Morales *et al* [101]	Double-blind placebo controlled cross-over trial	9 men/10 women, 50-65 yrs	100 mg oral DHEA daily six months and six months of placebo	DHEA supplements induces an increase serum IGF-I levels in both genders but dimorphic responses were evident in fat body mass and muscle strength in favour of men.
Percheron *et al* [102]	Randomized and placebo controlled	280 healthy ambulatory and independent men and women aged 60 to 80 years	12 months of placebo or DHEA treatment 50 mg/d, PO	No positive effect inherent to DHEA treatment was observed either on muscle strength or in muscle and fat cross-sectional areas.
Nair *et al* [103]	Randomized and placebo controlled	87 elderly men with low levels of the sulfated form of DHEA and bioavailable testosterone and 57 elderly women with low levels of sulfated DHEA.	Men: 29 received DHEA (75 mg/d tablet), 27 received testosterone (5 mg/d patch), and 31 received placebo. Women: 27 received DHEA (50 mg/d tablet) and 30 received placebo.	Neither DHEA nor low-dose testosterone replacement in elderly people has physiologically relevant beneficial effects on body composition, physical performance, insulin sensitivity, or quality of life.
Muller *et al* [104]	Randomized and placebo controlled	100 healthy, independently living men, aged 70 yr and over with low scores on strength tests.	Four arms: 1) atamestane (100 mg/d) and placebo; 2) DHEA (50 mg/d) and placebo; 3) Atamestane (100 mg/d)+DHEA (50 mg/d); 4) Two placebo tablets. 36 weeks.	Hormone replacement with DHEA and/or atamestane don´t improve the course of frailty.
Villarreal *et al* [105]	Randomized and placebo controlled	56 men and women. 65-78 years.	DHEA or placebo during 10 months and exercise during 4 latest months.	DHEA alone did not significantly increase strength or thigh muscle volume. DHEA therapy potentiated the effect of weightlifting training on muscle strength, evaluated by means of one-repetition maximum measurement and Cybex dynamometry, and on thigh muscle volume, measured by magnetic resonance imaging.

10 days of each 28-day cycle [HRT]; men: testosterone enanthate, biweekly intramuscular injections of 100 mg) (n = 35); 2) GH + placebo sex steroid (n = 30); 3) sex steroid + placebo GH (n = 35); or 4) placebo GH + placebo sex steroid (n = 31). The results showed that only the combined treatment of sex steroids plus GH had a marginal effect (increased) on the muscle strength and VO_{2max} in men, but not in women. GH alone increased lean body mass and decreased fat mass. Because the adverse events were most frequent and relevant in the group of GH replacement (mainly in relation with glucose metabolism), the risk-benefit ratio did not allow recommending the interventions with GH supplements in elderly people [110].

More recently, Sattler has published a RCT in which one hundred and twenty two community dwelling men, 71 years of age and older with a low plasma levels of both testosterone and IGF-1 were allocated to a treatment with transdermal testosterone (5 or 10 g/daily) plus GH (0, 3 or 5 mcg/Kg daily) for 16 weeks. In this study, a significant benefit in total and appendicular lean mass, muscle strength and aerobic endurance was demonstrated in the testosterone group. In addition, the outcomes appeared to be improved with concomitant treatment with GH replacement [111].

Insulin Like Growth Factor-1 (IGF-1)

As mentioned previously GH acts on skeletal muscle, which is responsible for 25% of the total production of IGF. It would therefore be reasonable to conclude that an IGF-1 supplement would produce an improvement in skeletal muscle function. However, results of the few clinical trials that have studied this have shown controversial results. Furthermore the characteristics of the population included in these trials make extrapolation difficult of its favourable results to an older population. As it is also the case with other substances (for instance, testosterone) this seems to offer some benefits. One explanation for the paucity of trials with IGF-1 in older people is the limitation in the doses to be used due to adverse effects.

Friedlander *et al*. published a randomized placebo controlled trial to determine the impact of 1 yr of IGF-I hormone replacement therapy on body composition, bone density, and psychological parameters in 16 healthy women over 60 years of age (112). Women were allocated to an injection of IGF-I (15 microg/kg twice daily) or the placebo group. The results did not show any differences between the two groups in bone mineral density of the forearm, lumbar spine, hip, and whole body mass [as measured by dual-energy x-ray absorptiometry (DXA)] nor in lean mass, fat mass, or percentage of body fat. Muscle strength was not different between two groups [112].

In contrast, Boonen *et al* published a RCT placebo controlled in 30 women (65-90 years old) immediately after a hip fracture (113). Women were allocated to a continuous administration of either placebo (n = 10), or rhIGF-I/IGFBP-3 at two different doses: 0.5 mg/kg.d (n = 9) or 1 mg/kg.d (n = 11) for 8 weeks after hip fracture surgery. IGF-1 was well tolerated, and no hypoglycemia or other side effects were observed. This study showed that IGF-1 induces a positive effect on functional recovery and increases the muscle strength without adverse events. However this is a small pilot trial and the results should be supported by future trials to further assess the therapeutic potential in this kind of population [113].

CONCLUSION

Although frailty is a common syndrome that causes numerous adverse health outcomes, the number of clinical trials focused on finding treatments to prevent or delay its development is scarce.

In this article we have reviewed the concept of frailty, the different pathophysiological mechanisms underlying frailty that could be potential therapeutic targets for intervention. Finally, we have reviewed the most relevant publications about new pharmaceutical treatment in frailty and sarcopenia focusing on clinical trials. At the moment, there is insufficient evidence for recommending the pharmacological treatment of frailty based on clinical trials.

Only in the case of testosterone supplements in men with low plasma levels of testosterone, there is sufficient evidence for recommendation about its use. Regarding other potential treatments, further large clinical trials are necessary to establish a recommendation about the pharmacological approach to frailty. In addition, there is a disappointing lack of trials of enough quality or with an acceptable sample size assessing potential pharmacological targets like antioxidant, anti-inflammatory substances, nutritional supplements or hormones. This gap of knowledge is one of the challenges to be faced during the next years in our aging societies to reach the objectives of both prolonging the healthy life expectancy and to enjoy a successful aging, free of disability.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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Association between endothelial dysfunction and frailty: the Toledo Study for Healthy Aging

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Abstract Cardiovascular disease (CVD), both clinical and subclinical, has been proposed as one of the mechanisms underlying frailty. However, there is no evidence addressing the relationship between the earliest stage of CVD (endothelial dysfunction) and frailty. The goal of the study was to analyze the association between endothelial dysfunction, evaluated by asymmetric dimethylarginine (ADMA) levels, and frailty. We used data from the Toledo Study for Healthy Aging, a prospective Spanish cohort study. Biological samples were obtained and ADMA levels were determined using an enzyme immunoassay method. Logistic regression was used to estimate the odds ratio (OR) and 95 % confidence intervals of frailty associated with ADMA. Adjustments were made for age, gender, cardiovascular risk factors, and presence of atherosclerotic disease (assessed by ankle–brachial index; ABI). One thousand two hundred eighty-seven community-dwelling elderly were included. One hundred seven (8.3 %) were identified as frail, 542 (42.1 %) as pre-frail, and 638 (49.6 %) as non-frail. ADMA values were higher in frail subjects than in non-frail ones. In addition, an interaction between the presence of atherosclerotic disease and ADMA on the odds of frailty (p=0.045) was detected. After adjustments for age, classical cardiovascular risk factors, and ABI, the risk of frailty was associated with increasing levels of ADMA in subjects without atherosclerotic disease [OR for 1 standard deviation increase in ADMA=1.14 (1.01–1.28), p=0.032] but not in those with atherosclerotic disease. In our study, endothelial dysfunction, assessed by ADMA levels, is associated with frailty. These findings provide additional support for a relevant role of vascular system since its earliest stage in frailty.

Keywords Frailty · Cardiovascular disease · Endothelial dysfunction · Asymmetric dimethylarginine · ADMA · Aging

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Background

In the last decades, the concept of frailty has emerged as an important condition associated with advanced age (Fried et al. 2001). It is a clinically recognizable state characterized by a reduced functional reserve and

impaired adaptive capacity across multiple physiologic systems predisposing to falls, fractures, functional impairment, institutionalization, and death (Fried et al. 2001; Rodriguez-Mañas et al. 2012). Gill and colleagues (2006) were the first in suggesting that frailty is a reversible process thus opening new targets in disability prevention and elderly care.

The physiological changes underlying frailty are difficult to identify (Walston et al. 2006). Alterations in several physiological systems have been suggested, including neuroendocrine dysregulation, decreased musculoskeletal functioning, immunological impairment, inflammation, and cardiovascular disease (CVD) (Carcaillon et al. 2012a; Carcaillon et al. 2012b; Barzilay et al. 2007; Newman et al. 2001). The relation between frailty and CVD has been shown not only for clinical diseases like stroke, infarction, angina, or intermittent claudication but also for subclinical manifestations (Newman et al. 2001).

The endothelium plays a crucial role in the vascular physiology and in the mechanisms leading to vascular diseases (Sitia et al. 2010). Previous studies demonstrated that endothelial dysfunction precedes atherosclerotic disease and predicts future cardiovascular events (Sitia et al. 2010; El Assar et al. 2012; Najjar et al. 2005). Among several substances and mediators, nitric oxide (NO) has been extensively studied as one of the most relevant factors released by the endothelium, playing an outstanding role in maintaining the function of the vascular system (El Assar et al. 2012). Reduced NO bioavailability is one of the changes usually observed in endothelial dysfunction and leading to vascular disease (El Assar et al. 2012). Asymmetric dimethylarginine is an endogenous inhibitor of NO synthase (Cooke 2005) commonly used as a marker of endothelial dysfunction (Stuhlinger et al. 2003). Many studies have shown that increased concentrations of asymmetric dimethylarginine (ADMA) was present in several conditions associated to endothelial dysfunction including aging, hypercholesterolemia, hypertension, diabetes mellitus, obesity, hyperhomocysteinemia, and renal failure (Sibal et al. 2010). Furthermore, in prospective studies, increased ADMA concentration has been identified as an independent risk factor for progression of atherosclerosis and cardiovascular death (Meinitzer et al. 2007).

Although the association between CVD (clinical and subclinical) and frailty is well established, there are no studies assessing the relation between endothelial dysfunction (the earliest form of subclinical CVD) and frailty. The goal of this study was to analyze the relationship between endothelial dysfunction, evaluated by ADMA levels, and frailty.

Methods

Study population

The Toledo Study for Healthy Aging (TSHA) is a Spanish longitudinal population-based study, designed for evaluating the determinants of physical frailty in the elderly. The used methodology has been reported previously (Garcia-Garcia et al. 2011). Participants in the TSHA come from two sources. The first one, called "the historic cohort," is formed by the survivors of a previous study (The Toledo Study), a population of subjects being over 77 years in 2006 (Garcia Garcia et al. 2001). Individuals 65–76 years old in 2006, specially recruited for the TSHA study, form the second one, called "the new cohort." Subjects from both sources were selected by a two-stage random sampling from the municipal census of Toledo, covering institutionalized and community-dwelling people from rural and urban settings. All subjects underwent the same assessment.

Data were collected between June 2006 and September 2009. Firstly, trained psychologists went to the subjects' house to fill in questionnaires with extensive information on sociodemographic characteristics, social support, dependence in activities of daily living, physical activity, health related quality of life, depressive symptoms, and cognitive function. In addition, data about prevalent disease, including cardiovascular risk factors (hypertension, diabetes, obesity, and hypercholesterolemia) and CVD were collected by self-reporting. Subsequently, enrolled subjects underwent a complete physical exam by a team of nurses. They evaluated the heart rate, blood pressure, anthropometric measures, ankle–brachial index, and physical performance (walk speed, upper and lower extremities strength, balance, and the stand-and-sit from a chair test). Finally, study participants went to their health center to provide a fasting blood sample.

The study protocol was approved by the Clinical Research Ethics Committee of the Complejo Hospitalario de Toledo, Spain. All study participants gave a signed informed consent prior to their inclusion in the cohort.

Blood collection and measurements

At baseline, blood samples were obtained from all subjects (45 cm^3 of blood while fasting). Within 2 h since drawing, samples were taken to the laboratory in containers at a temperature between 2 and 4 °C, and then they were divided in aliquots with EDTA and stored at −80 °C. Asymmetric dimethylarginine was measured in the Research Unit of the Hospital Universitario de Getafe (Madrid, Spain). ADMA levels were determined using a validated enzyme immunoassay method (Schulze et al. 2004) with expected values between 0.4 and 0.75 μmol/l (80–150 ng/ml) and a sensitivity of 0.05 μmol/l. The coefficients of inter-assay variation were 9.8 to 10.3 % for lower levels and 8.3 to 9.4 % for higher levels. The coefficients of intra-assay variation were 5.7 to 6.4 %.

Frailty measure

Frailty was assessed using Fried's criteria (Fried et al. 2001), but using cutoff points for slowness, weakness, and low physical activity adapted to the characteristics of our population (see later). Five items compose this scale: slowness, weakness, weight loss, exhaustion, and low physical activity. The method of measuring every item has been described elsewhere (Garcia-Garcia et al. 2011). Slowness was defined using the 3-m walking speed test; individuals were asked to walk 3 m at their usual pace, following a standardized protocol; sex- and height-adjusted time points were used; the slowest quintile was considered positive. Weakness was measured by grip strength in the dominant hand using a Jamar hydraulic dynamometer; the result was adjusted by the subject's body mass index; those in the bottom quintile were considered positive for this criterion. Weight loss was considered positive for reporting more than 4.5 kg of unintentional weight loss in the previous year. Exhaustion was assessed using two questions ("I felt that anything I did was a big effort" and "I felt that I could not keep on doing things"); answers were scored between 0 and 4 depends on symptoms' frequency; if any question was answered 2 or higher, this criterion was considered positive. Low physical activity was based on the Physical Activity Scale for the Elderly (Schuit et al. 1997); those in the worse quintile of physical activity were considered positive for this item. Subjects were classified as frail if they met three or more of these items, as pre-frail if subjects met one or two criteria, and non-frail or robust if none item was present.

Atherosclerotic disease definition

Atherosclerotic disease was considered as a self-reported history of stroke, myocardial infarction, angina pectoris, or intermittent claudication. Subclinical atherosclerotic disease was assessed by ankle–brachial index (ABI). For this purpose, blood pressure was determined, in all patients, in both arms and ankles (posterior tibial artery and dorsalis pedis artery) with the patient supine for at least 5 min before, using a standard sphygmomanometer and a handheld Doppler ultrasound (Vascular Pocket Doppler Model 841-A; Parks Medical Electronics, Inc, Aloha, OR). A cycle of measurements (right arm, right ankle, left ankle, and left arm) was repeated, and the means of two measurements for each limb were used. Finally, the ratio of the highest systolic pressure in the ankle to the higher of the left or right brachial systolic pressure was used to define the ABI (Espinola-Klein et al. 2008; Hirsch et al. 2006). The participants were classified by their ABI according to the ACCF/AHA 2011 Guidelines (ACCF/AHA 2011) (Table 1).

Statistical analysis

Subject's characteristics according to frailty status were compared using Pearson Chi-square tests. ADMA was log-transformed to normalize its distribution. Levels of ADMA according to subjects' characteristics are consequently displayed as geometric means and interquartile range. GM comparisons were performed using standard Student *t* tests for dichotomous variables and using ANOVA for variables with more than two categories. Odds ratio (OR) and 95 % confidence interval (95 % CI) of frailty (versus robust and pre-frail) associated with ADMA were estimated using logistic regression. OR were estimated for 1 standard deviation (SD) increased in ADMA as well as for quartiles. Test for linear trend across quartiles are displayed. In addition, deviation from linearity was assessed using appropriate log-likelihood tests. Adjustments were made for classical cardiovascular risk factors (age, sex, hypertension, diabetes, hypercholesterolemia, and BMI), the presence of atherosclerotic disease (clinical and subclinical), and the renal function. Multiplicative interactions between ADMA and adjustment variables were systematically

Table 1 Subject's characteristics according to Frailty Status (n=1,287)

	Total	Robust (n=638)		Pre-frail (n=542)		Frail (n=107)		p value
		n	%	n	%	n	%	
Sex Male	552	275	43.1	241	44.5	36	33.6	0.117
Age groups (years)								
<75	685	415	66.1	248	45.8	22	20.6	<0.0001
[75–80]	397	169	26.5	190	35.1	38	35.5	
≥80	205	54	8.5	104	19.2	47	43.9	
Educational level								
No formal schooling	860	392	61.7	391	72.1	77	72.0	0.002
Uncompleted school	225	125	19.7	81	14.9	19	17.8	
Primary or secondary school	199	118	18.6	70	12.9	11	10.3	
BMI categories (kg/m^2)								
<25	193	77	12.1	96	17.8	20	18.9	<0.0001
[25–30]	556	302	47.6	218	40.5	36	33.9	
≥30	530	256	40.3	224	41.6	50	47.2	
HTA	665	331	52.6	277	51.3	57	54.3	0.817
Hypercholesterolemia	491	245	39.5	207	38.9	39	37.5	0.927
Diabetes	240	103	16.4	113	21.0	24	23.1	0.069
Atherosclerotic disease	183	67	10.5	86	15.9	30	28.0	<0.0001
Ankle–brachial index								
≤0.9	238	111	18.0	99	19.0	28	28.3	0.906
0.9–1.0	322	155	25.2	139	26.7	28	28.3	
1.0–1.4	647	336	54.6	271	52.1	40	40.4	
>1.4	28	14	2.3	11	2.1	3	3.0	

tested before adjusting for this variable. As we detected an interaction between the presence of atherosclerotic disease and ADMA, results are given in both strata separately.

Results

Study population

One thousand two hundred eighty-seven persons (552 men and 735 women) composed our study population. The mean age was 74.4 (5.4) years. Table 1 displays the sample characteristics according to frailty status and the Table 2 shows the ADMA levels according to subject characteristics. Overall, 18.8 % of the subjects were diabetic, 52.1 % had hypertension, 39.0 % had hypercholesterolemia, and 41.4 % were obese. Regarding clinical atherosclerotic diseases, 401 diagnoses of angor, myocardial infarction, stroke, or intermittent claudication, either isolated or in combination, were collected. Women had more comorbidities than men 1.7 (SD=1.1) versus 1.4 (SD=1.1), p<0.0001. Frailty was associated with older age (p<0.0001), lower educational level (p=0.002), BMI (p<0.0001), and presence of atherosclerotic disease (p<0.0001).

When we assessed levels of ADMA according to subject's characteristics (Table 2), we found differences in ADMA values according to the frailty status (p=0.045) as well as according to age, sex, and education level. There was no association with classical risk factors neither with clinical CVD.

Effect of the endothelial dysfunction on the relationship between ADMA and frailty

There was an interaction between ADMA levels and atherosclerotic disease on the odds of frailty (p=0.045).

Table 2 Levels of ADMA according to subject's characteristics

	n	%	GM	IQR	*p* value[a]
Sex					
Male	552	42.8	0.77	(0.63;0.92)	0.025
Female	735	57.1	0.79	(0.65;0.98)	
Age groups (years)					
<75	685	53.2	0.75	(0.63;0.92)	<0.0001
[75–80]	397	30.8	0.80	(0.65;0.97)	
≥80	205	15.9	0.85	(0.69;1.02)	
Educational level					
No formal schooling	860	66.9	0.79	(0.67;0.96)	0.022
Uncompleted school	225	17.5	0.74	(0.61;0.92)	
Primary or secondary school	199	15.4	0.77	(0.63;0.96)	
BMI categories (kg/m^2)					
<25	193	15.0	0.77	(0.67;0.91)	0.469
[25–30]	556	43.4	0.79	(0.65;0.97)	
≥30	530	41.4	0.77	(0.65;0.95)	
HTA					
No	609	47.8	0.78	(0.65;0.95)	0.520
Yes	665	52.1	0.77	(0.65;0.94)	
Hypercholesterolemia					
No	766	60.9	0.79	(0.65;0.97)	0.080
Yes	491	39.0	0.77	(0.65;0.93)	
Diabetes					
No	1,031	81.1	0.78	(0.65;0.96)	0.102
Yes	240	18.8	0.76	(0.63;0.91)	
Atherosclerotic disease					
No	1,104	85.8	0.79	(0.65;0.95)	0.940
Yes	183	14.2	0.79	(0.65;0.98)	
Ankle–brachial index					
≤0.9	238	19.3	0.78	(0.65;0.95)	0.906
0.9–1.0	322	26.1	0.79	(0.65;0.98)	
1.0–1.4	647	52.4	0.78	(0.65;0.95)	
>1.4	28	2.2	0.79	(0.63;0.90)	
Frailty					
No frail	638	49.5	0.78	(0.65;0.94)	0.045
Pre-frail	542	42.1	0.79	(0.64;0.95)	
Frail	107	8.3	0.84	(0.70;1.02)	

GM Geometric mean, *IQR* Inter Quartile Range

[a] Estimated from linear regression with the log transformation of ADMA as the dependent variable.

In subjects without clinical atherosclerotic disease, the mean ADMA levels were significantly higher in frail than in pre-frail or non-frail subjects [*M*=0.83 (SD=0.26), *M*=0.77 (SD=0.26), and *M*=0.78 (SD=0.23) respectively, *p* for difference=0.032]. In contrast, we did not find any statistically significant relationship in subjects with clinical atherosclerotic disease (*p*=0.324) (Fig. 1).

To further evaluate the relationship between endothelial dysfunction and frailty, multivariate analyses were performed separately in subjects with and without clinical CVD. After adjustment for classical cardiovascular risk factors, there was a significantly increased risk of frailty associated with increased ADMA levels (*p* for trend=0.032) in subjects without clinical CVD, but not in those with clinical CVD (Table 3). Further adjustment for ABI, an objective measurement of subclinical atherosclerotic disease, did not substantially modify the results. The risk of being frail increased as did the concentration of ADMA, being doubled for the subjects in the highest quartile [2.09, 95 % CI (0.95–4.61), *p* for trend=0.018] (Table 3). Finally, as ADMA levels can be modified by the presence of kidney dysfunction, we make a final adjustment by creatinine levels. This last adjustment did not produce any significant change in the association trend [2.05, 95 % CI (0.92–4.51), *p* for trend=0.021] (Table 3). Again, no relationship was found in subjects with clinical CVD. We did not identify any significant interaction between other subjects' characteristics and ADMA on the odds of frailty.

Discussion

In the present paper, we show for the first time an association between frailty and endothelial dysfunction. These findings not only reinforce the known relationship between frailty and CVD (clinical and subclinical) but also support that this relation exists since a very early stage when only the endothelial dysfunction is present.

The existence of a relationship between the vascular system and frailty has been claimed since more than a decade. However, the precise stage of the vascular disease from which this association is present remains unclear although it may be of great clinical relevance as to target populations suitable for intervention and prevention. The first data showing an association between frailty and CVD were published in a secondary analysis of the Zutphen Elderly Men's Study in 1999 [OR for CVD in frail men=4.1, 95 % CI (1.8–9.3)] (Chin et al.

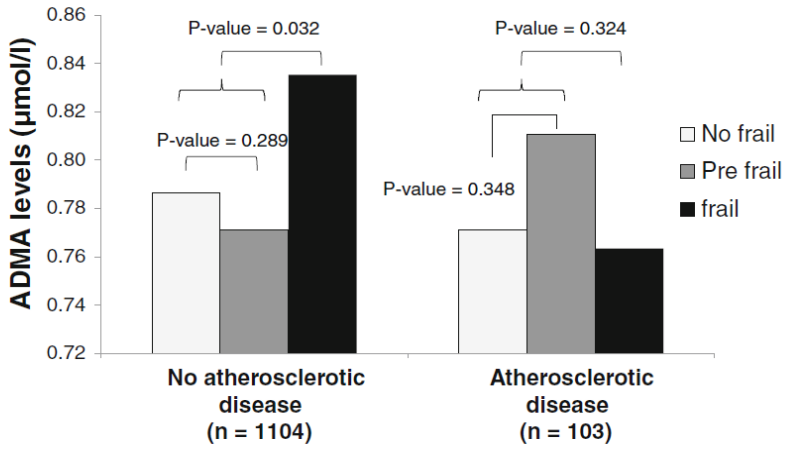

Fig. 1 Age-adjusted geometric means of ADMA in frail, pre-frail, and non-frail subjects with and without atherosclerotic disease

1999). Later, in 2001, data from the Cardiovascular Health Study confirmed this relationship [OR=2.79, 95 % CI (2.12–3.67)] (Newman et al. 2001). The Women's Health Initiative Observational Study was the first and largest study to find that CVD was a risk factor for developing incident frailty (Woods et al. 2005). Furthermore, epidemiological data reinforce these findings in different settings and with different frailty scores (Newman et al. 2006; Purser et al. 2006). Only one previous study (the Cardiovascular Health Study (Newman et al. 2001)), reported an association between subclinical CVD and frailty. In this study, the presence of different biomarkers of CVD in absence of clinical manifestations was associated with frailty.

ADMA reduces NO production by a competitive inhibition of endothelial nitric oxide synthase (eNOS) (Cooke 2005). NO induces vasodilatation and inhibits platelets aggregation, adhesion of monocytes and leukocytes to the endothelium, smooth muscle cell proliferation, oxidation of LDL, and vascular inflammation by suppressing the expression and activity of adhesion molecules and chemokines, protecting the vascular wall from different stresses and injuries (Sibal et al. 2010). As a consequence, when ADMA levels increases, endothelial dysfunction appears and, if it is maintained along the time, subsequent atherosclerosis develops (Cooke 2005). Several studies done in patients with hypertension and hypercholesterolemia showed ADMA levels inversely correlated to the endothelial dependent vasodilatation, measured by brachial artery flow (Achan et al. 2003; Perticone et al. 2005). All these studies have reported ADMA as a novel marker of endothelial dysfunction. Furthermore, in prospective studies, increased ADMA levels were strong predictors of cardiovascular events and mortality not just in patients with cardiovascular risk factors and CVD but also in healthy people (Schulze et al. 2005).

Increased concentration of ADMA by age and impaired renal function are usual findings (El Assar et al. 2012; Xiao et al. 2001; Kielstein et al. 2003). However, they do not seem to account for our findings since both variables have been included in the adjusted multivariant models, without changing the association between ADMA and frailty in older people without CVD.

Moreover, although not directly accounting for this relationship, some common mechanisms may explain, at least partially, the direct relationship between ADMA levels and frailty. One of the most constant findings in frail people is an increase in inflammation and in oxidative stress (Mulero et al. 2011). And these two same mechanisms have been related to a decrease in the vascular level of dimethylarginine dimethylaminohydrolase (DDAH), the key enzyme for ADMA metabolism (Teerlink 2005).

It has been demonstrated that increased ADMA concentration is associated with reduction of DDAH expression in some cardiovascular diseases such as atherosclerosis and hypertension (Chen et al. 2013).

Table 3 Odds (95 % CI) of frailty associated with ADMA by atherosclerotic diseases status

	Atherosclerotic diseases					
	No (n=1,104)		p value	Yes (n=183)		p value
	OR	95 % CI		OR	95 % CI	
Model 1[a]						
For 1 SD increase	1.18	(1.07–1.31)	0.001	0.97	(0.83–1.14)	0.735
Quartiles	Ref			Ref		
	1.27	(0.58–2.79)	0.551	1.26	(0.42–3.73)	0.679
	1.70	(0.79–3.65)	0.173	0.81	(0.27–2.45)	0.713
	2.85	(1.40–5.83)	0.004	0.80	(0.28–2.58)	0.778
p for trend			0.001			0.619
Model 2[b]						
For 1 SD increase	1.13	(1.01–1.26)	0.032	0.91	(0.76–1.10)	0.324
Quartiles	Ref			Ref		
	1.00	(0.44–2.26)	0.995	1.28	(0.41–4.02)	0.668
	1.26	(0.57–2.78)	0.564	0.69	(0.22–2.20)	0.529
	2.07	(0.99–4.33)	0.055	0.66	(0.21–2.15)	0.494
p for trend			0.022			0.342
Model 3[c]						
For 1 SD increase	1.12	(1.00–1.25)	0.049	0.89	(0.73–1.10)	0.286
Quartiles	Ref			Ref		
	1.08	(0.47–2.51)	0.859	1.72	(0.49–6.06)	0.402
	1.46	(0.64–3.31)	0.368	0.62	(0.17–2.29)	0.475
	2.06	(0.94–4.49)	0.070	0.65	(0.18–2.40)	0.519
p for trend			0.032			0.342
Model 4[d]						
For 1 SD increase	1.14	(1.01–1.28)	0.032	0.84	(0.67–1.04)	0.110
Quartiles	Ref			Ref		
	0.88	(0.37–2.13)	0.782	1.90	(0.51–7.11)	0.341
	1.51	(0.66–3.44)	0.328	0.56	(0.14–2.28)	0.422
	2.09	(0.95–4.61)	0.067	0.39	(0.09–1.69)	0.207
p for trend			0.018			0.104
Model 5[e]						
For 1 SD increase	1.35	(1.02–1.79)	0.035	0.64	(0.38–1.10)	0.105
Quartiles	Ref			Ref		
	0.87	(0.36–2.09)	0.749	2.07	(0.55–7.71)	0.280
	1.45	(0.63–3.31)	0.382	0.49	(0.12–1.99)	0.315
	2.05	(0.92–4.51)	0.076	0.39	(0.09–1.70)	0.210
p for trend			0.021			0.098

[a] Crude

[b] Adjusted for age

[c] Adjusted for age, hypertension, hypercholesterolemia, diabetes, sex, and BMI categories

[d] Adjusted for age, hypertension, hypercholesterolemia, diabetes, sex, BMI categories, and ABI categories

[e] Adjusted for age, hypertension, hypercholesterolemia, diabetes, sex, BMI categories, ABI categories, and renal function

DDAH exists in two isoforms DDAH-1 and DDAH-2 with distinct tissue-relevant distribution. DDAH-1 is predominantly expressed in tissues expressing neuronal nitric oxide synthase, whereas DDAH-2 is located mainly in vasculature tissues containing the eNOS isoform. It was shown that DDAH-2 is inhibited by reactive oxygen species leading to ADMA accumulation (Ito et al. 1999). Furthermore, the expression of

DDAH has been shown to be reduced in endothelial cells pretreated with TNF-α (Ito et al. 1999).

The association between endothelial dysfunction and frailty strengthen the role of vascular disease in frailty, suggesting that it would be relevant since the very early stages of vascular dysfunction when only functional impairment (endothelial dysfunction) is apparent. This fact opens new perspectives in the field of frailty. First, these results offer new views to the interpretation of some research results regarding frailty. Until now, different observational studies have shown a relationship between immunological and thrombosis biomarkers (factor VIII, D-dimer, C-reactive protein, low hemoglobin, high leukocytes, high fibrinogen…) with both CVD and frailty showing possible mechanistic links between them (Phan et al. 2008; Walston et al. 2002). However, many of these factors are also related to endothelial dysfunction, thus supporting a potential role for endothelial dysfunction in the pathophysiology of frailty. In this regard, it is interesting to note that aging per se induces endothelial dysfunction, in absence of cardiovascular risk factor and CVD (Rodriguez-Mañas et al. 2009; Angulo et al. 2012). The mechanism of this age-associated endothelial dysfunction has two complementary sources: an increased oxidative stress and a pro-inflammatory profile (Rodriguez-Mañas et al. 2009). As it has been previously stated, these two mechanisms are also related to both increased plasma levels of ADMA and frailty, suggesting a common underlying mechanism. Unfortunately, we did not measure these biomarkers that could be of utility to support this pathophysiological link. Second, our results suggest that ADMA, in addition to be a risk marker of endothelial dysfunction and a strong predictor of CVD, might be a novel marker of frailty in patients without CVD. This opens new alternatives for elderly care, including both the treatment and prevention of frail older people. In this regard, a necessity to identify potential biomarkers of frailty useful to improve the diagnosis and prognosis of this syndrome has been claimed by different groups of experts. In addition, recent literature proposes ADMA as a target for pharmacotherapy in diseases and conditions that are different from CVD but in which endothelial dysfunction may be involved (Sibal et al. 2010; Beltowski and Kedra 2006). The fact that we did not find any association between ADMA and frailty among subjects with clinical atherosclerotic disease may be due to the weight of clinical CVD in determining frailty, making undetectable the effect of the endothelial dysfunction on frailty when the symptomatic disease is present. Regarding subclinical CVD, the association between endothelial dysfunction and frailty is independent of its presence, as it remains after adjusting for this factor. As a whole, this picture draws a scenario where pathological changes in the cardiovascular system are involved in mechanisms leading to frailty since their earliest stages, with the heaviest role for clinical CVD but with relevant roles for both subclinical CVD and endothelial dysfunction.

Our study presents some strengths and limitations. As strengths, we have evaluated this relationship in the TSHA cohort. This study is being carried out on a large population-based sample of subjects (Garcia-Garcia et al. 2011). Frailty was measured using Fried's clinical criteria, one of the most validated frailty scales, but fitted to the profile of our population. This adjustment of the cutoff point for meeting the diagnostic criteria is important when you are working on populations phenotypically different from the ones where frailty criteria were originally described. There is some literature where it was found that the prevalence of frailty was really discordant between different countries using the same cutoff points as those used for the US population (Santos-Eggimann et al. 2009). For avoiding these differences, the main studies that assess the frailty phenotype in different settings, which is with different populations, use the LP Fried criteria but standardizing them to their own populations (continuous variables are thus considered positive when the subject belongs to the lowest quintile in its own population not in the US population) (Espinoza et al. 2010). Otherwise, the risk for misestimating frailty is really high (Rodriguez-Mañas et al. 2012; Bergman et al. 2007; Santos-Eggimann et al. 2009). To avoid misdiagnosis of frailty, we adapted the cutoff points for the three items highly dependent on the characteristics of the individuals (gait velocity, grip strength, and physical activity) to our population, maintaining the criteria to meet each one of the items (Percentile 20 of the distribution) as originally described. The measurements were performed by skilled, trained, certified researchers. We used ADMA as a marker of endothelial dysfunction. Although a direct assessment of endothelial function is the "gold standard," its use in epidemiological studies with many participants presents relevant challenges that can be overcome by the use of biomarkers like ADMA. ADMA has been used in several recent studies (not only epidemiological but also in little cohorts of individuals or in case–control studies) as a reliable biomarker of endothelial function (Hsu et al.

2012; Rentoukas et al. 2012; Dogru et al. 2012). ADMA determinations were performed using a validated quantitative determination by enzyme immunoassay (Schulze et al. 2004). All determinations were performed twice to reduce the risk of error variation.

The two main limitations of our results are its cross-sectional design, which does not allow us to conclude in terms of causality and the self-reported nature of the information regarding the presence of CVD. Nonetheless, self-report data have been extensively used in epidemiological studies although some authors have claimed that they underestimated the true prevalence of disease (Espelt et al. 2012). A bias of the results based on the differential misclassification of the subjects according to their cardiovascular status is unlikely so this issue may only lead to underestimate the association of ADMA with frailty among subjects without atherosclerosis. Moreover, the tendency observed in the group of self-reported atherosclerotic disease goes in the opposite direction, decreasing the OR as ADMA increases and, anyway, far from the statistical significance. In addition, we further adjusted our model for a robust surrogate of the presence of atherosclerosis (ABI), which remains as a good biomarker of subclinical atherosclerosis (Berni et al. 2011; Lim et al. 2013; Zhang et al. 2013) and the renal function, estimated by the creatinine levels, because of the kidney metabolism of the ADMA. The possible remaining variability due to these factors has been taken into account in the last models, showing no differences in the association.

In conclusion, we show for the first time a relationship between endothelial dysfunction and frailty in older people. These findings provide additional support for a relevant role of vascular system in frailty since the early stages of vascular disease that, if confirmed, should raise new targets for detection, intervention, and prevention of frailty.

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Original Study

The Standardization of Frailty Phenotype Criteria Improves Its Predictive Ability: The Toledo Study for Healthy Aging

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A B S T R A C T

Introduction: Several studies have assessed the performance of the original frailty phenotype criteria (FPC) and the standardized version according to the characteristics of the population. No studies exist, however, evaluating the impact of this standardization on its predictive ability.

Objective: To compare how the original FPC and the standardized-frailty phenotype criteria (S-FPC) estimate the prevalence of frailty and their ability to predict mortality, hospitalization, incident disability, and falls.

Methods: Data were taken from the Toledo Study for Healthy Aging, a population-based, community-dwelling study conducted on 1645 individuals over 65. Frailty was operationalized in two ways: FPC, using the cut-off estimated in the Cardiovascular Health Study and S-FPC, using cut-off points fitted to the phenotypic characteristics of our study sample. Frailty prevalences were compared using chi-square statistic. Cox proportional hazard models and logistic regressions evaluated the predictive ability of both tools. Lastly, survival tests were applied.

Results: Frailty and prefrailty prevalences varied according to the tool used: 24.12% and 66.40%, respectively when we used FPC and 6.68% and 47.81% when we used S-FPC ($P < .01$). Regarding their predictive ability, S-FPC, but not FPC, identified consistently the prefrail persons as an intermediate risk group between robust and frail people [death 1.57 (1.15-2.16); hospitalization 1.47 (1.16-1.85); and incident disability 1.96 (1.30-2.97); $P < .005$]. Furthermore S-FPC predicted death and hospitalization at shorter times than FPC ($P < .05$).

Conclusion: FPC should be standardized according to the characteristics of the population in order to improve its predictive ability.

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Frailty is a biologic syndrome characterized by a decreasing reserve and resistance to stressors that increases the vulnerability to adverse events.[1,2] It follows a dynamic course with frequent transitions over time,[3] modulated by several factors.[4,5] Additionally, some interventions have been developed to improve clinical outcomes in frail patients,[6,7] making frailty an important target to address in older adults.[8] Therefore, there is an urgent need to find the most appropriate diagnostic tools.[9–11]

Many instruments have been shown to identify frailty.[1,12–20] Among them, the frailty phenotype is the most widely used tool in

Table 1
Criteria Used to Define Original FPC and S-FPC

	FPC	S-FPC
Weight loss	In the last year, have you lost more than 10 pounds (4.54 kg) unintentionally?	
	☐ No ☐ Yes	
	If answer is yes, this criterion is positive.	
Exhaustion	Using the CES-D, the following two statements are read asking how often in the last week did you feel this way?	
	• I felt that everything I did was an effort	
	• I could not get going	
	0 = rarely or none time (<1 day)	2 = a moderate amount of the time (3–4 days)
	1 = some or little time (1–2 days)	3 = most of the time
	Persons answering "2" or "3" to either of these questions are categorized as positive.	
Slowness	Gait speed stratified by gender and height	
	Men	Men
	Height ≤173 cm…≤ 0.76 m/s	Height ≤164 cm…≤0.5 m/s
	Height >173 cm…≤ 0.65 m/s	Height >164 cm…≤0.43 m/s
	Women	Women
	Height ≤159 cm…≤0.76 m/s	Height ≤152 cm…≤0.41 m/s
	Height >159 cm…≤0.65 m/s	Height >152 cm…≤0.33 m/s
	If gait speed is lower than these respective cut-offs, the criterion is positive	
Weakness	Grip strength stratified by gender and BMI quartiles:	
	Men	Men
	BMI ≤24…≤29 kg	BMI ≤25.5…≤19.1 kg
	BMI 24.1–26…≤30 kg	BMI 26.4–28…≤22.9 kg
	BMI 26.1–28…≤30 kg	BMI 28.1–30.8…≤22.9 kg
	BMI >28…≤32 kg	BMI >30.8…≤22.9 kg
	Women	Women
	BMI ≤23…≤17 kg	BMI ≤26.4…≤11 kg
	BMI 23.1–26…≤17.3 kg	BMI 26.5–29.5…≤12 kg
	BMI 26.1–29…≤18 kg	BMI 29.6–32.9…≤12 kg
	BMI >29…≤21 kg	BMI ≥33…≤12 kg
	If grip strength is lower than these respective cut-offs, the criterion is positive	
Low activity	Kcal of leisure physical activity stratified by gender:	
	Men <383 Kcal (to walk at least 2:30 hours per week).	Men <459.6 Kcal (to walk at least 3 hours per week)
	Women <270 Kcal (to walk at least 2 hours per week)	Women <135 Kcal (to walk at least 1 hour per week)
	If Kcal of leisure physical are under these respective cut-offs, the criterion is positive	

BMI, body mass index; CES-D, Center for Epidemiological Studies-Depression Scale; FPC, frailty phenotype criteria; S-FPC, standardized-frailty phenotype criteria.

the literature.[11] Some concerns have been raised however, when using these criteria in different settings and/or group of older persons, including large differences in the prevalence of frailty between countries and racial minorities.[21,22]

Some authors explain these issues pointing at economic or social factors,[21] but others have suggested that these differences could be due to phenotypic diversity, which is predominantly expressed in that criteria linked to physical function: weakness, slowness, and physical activity.[22] In this regard, it has been shown that when the assessed population is phenotypically different from the participants in the Cardiovascular Health Study (CHS), a misclassification of the frailty status may result simply because they differ significantly from the CHS group on the physical characteristics upon which the frailty phenotype criteria (FPC) were developed.[22]

Table 2
Descriptive Analysis: Baseline Characteristics

	All (n = 1645)	Frailty Phenotype Criteria			Standardized-Frailty Phenotype Criteria		
		Robust n = 157	Prefrail n = 1078	Frail n = 401	Robust n = 780	Prefrail n = 725	Frail n = 131
Age (years)	74 (70–78)	70 (68–74)	74 (70–77)	77 (73–81)	72 (69–76)	75 (72–79)	79 (75–83)
Sex (% men)	44.38	64.33	48.79	24.69	47.31	43.45	32.06
Height (cm)	157 (151–164)	162 (155–168)	158 (152–165)	152 (148–158)	158 (152–165)	156 (150–164)	153 (147–159)
BMI (kg/m^2)	28.83 (26.06–31.99)	27.33	28.65	30.06	28.72	28.76	29.78
Ch. Index (%)							
0	46.82	51.59	49.91	36.66	52.82	43.72	28.24
1	25.25	28.66	24.86	24.94	25.00	25.66	24.43
2	15.22	12.74	13.54	20.70	11.92	17.10	24.43
≥3	12.71	7.01	11.69	17.71	10.26	13.52	22.90
Disability (%)							
0	92.12	99.36	96.45	77.69	98.46	92.06	54.62
1	5.36	0	2.81	14.29	1.29	6.41	23.85
≥ 2	2.52	0.64	0.75	8.02	0.26	1.53	21.54
Cognitive st (%)							
≥ 24	57.05	83.69	60.08	35.60	66.57	51.48	25.25
19–23	33.14	15.60	33.26	40.78	27.76	38.03	40.40
≤ 18	9.81	0.71	6.65	23.62	5.67	10.49	34.34
Depression (%)	18.03%	7.09	11.75	38.07	8.26	22.38	50.41

BMI, body mass index; Ch. Index, Charlson Index; disability, self-reported disability in basic activities of daily living (bathing or showering, dressing, eating, getting in and out of bed, using the toilet); cognitive st, cognitive status (MMSE 0-30); depression, Geriatric Depression Scale ≥5.
Data are medians (25th, 75th percentile).

Table 3
Comparison of the Individual Classification According to the Scale Used

	Standardized-Frailty Phenotype Criteria		
	Robusts (n = 786)	Prefrails (n = 729)	Frails (n = 131)
Frailty Phenotype Criteria			
Robusts (n = 159)	159	0	0
Prefrails (n = 1086)	610	476	0
Frails (n = 401)	17	253	131

In fact, striking differences have resulted from large studies assessing the performance of the original FPC, as validated in CHS and the standardized version related to the characteristics of the population.[22] But this misclassification will be truly worthy if it results in changes in the assessment of the risk for adverse outcomes. At present, however, no study has evaluated the impact of this misclassification on the predictive ability of the FPC.

In this study, we will evaluate if the standardized-frailty phenotype criteria (S-FPC; according to the local characteristic of Spanish population) change the classification of community-dwelling older adults according to their frailty status and their ability to predict mortality, hospitalization, incident disability, and falls compared with the original FPC.

Methods

Population

The Toledo Study for Healthy Aging (TSHA) is a Spanish longitudinal population-based study, designed for evaluating the determinants of physical frailty in individuals older than 65 years of age, living in the Spanish city of Toledo. The used methodology has been reported previously.[23] All participants were selected by a two-stage random sampling from the municipal census of Toledo, covering institutionalized (1.9%) and community-dwelling (98.1%) people from rural and urban settings. They underwent identical baseline evaluations and follow-up.

The study protocol was approved by the Clinical Research Ethics Committee of the Toledo Hospital (Complejo Hospitalario de Toledo), Spain. Participants gave a signed informed consent prior to their inclusion in the cohort. People with available data on all the variables pertinent for the purposes of the present study were included (n = 1645 persons).

Operationalization of Frailty

Frailty phenotype was operationalized in two ways: FPC, using the cut-offs estimated in the CHS[1] and the S-FPC, using the same methodology as Fried and colleagues used in their original article where slowness, weakness, and physical activity were positive if the values are included in the lowest quintile of the study sample distribution. FPC and S-FPC cut-off values are presented in Table 1.

Slowness was defined using the 3-meter walking speed test. Individuals were asked to walk 3 meters at their usual pace twice. The best time was chosen; sex and height adjusted time points were used. *Weakness* was measured by grip strength using a Jamar hydraulic dynamometer in the dominant hand. After three repetitions, the best result was selected and adjusted by the person's body mass index. *Weight loss* was considered positive for reporting more than 4.54 kg of unintentional weight loss in the previous year. *Poor endurance and energy* was assessed by self-report of exhaustion using two questions ("How many days during the last week have you felt that anything you did was a big effort?" and "How many times during the last week have you felt that you could not keep on doing things?"). Answers were scored between 0 and 4 depending on symptom frequency; if any question was answered at a score of 2 or higher, this criterion was considered positive. *Physical activity* was assessed using the Physical Activity Scale for the Elderly (PASE)[24] instead of the Minnesota Leisure Time Activity questionnaire used on CHS. The adjustment has been made taking into account the amount of calories used for leisure activities.

Outcomes

Main outcomes were all causes of death, hospitalization, incident disability, and falls. To detect deaths, we used information from the National Mortality Database provided by the National Institute of Statistics along the follow-up period (mean, 5.5 years; range, 0.30–6.79 years). The hospital's database and telephone follow-up were used to detect hospitalizations at a mean follow-up of 3.5 years (range, 0.3–4.79 years). Incident disability was defined as the self-reported loss of at least one of the activities of daily living (ADL) during a mean follow-up period of 5.02 years (range, 4.8–5.2 years). The presence of falls was defined as referring at least one fall in the last year before the interview (mean follow-up, 5.02 years; range, 4.8–5.2 years).

Statistical Analysis

Descriptive statistics were used to summarize the data and raising the cut-off points for the S-FPC. For each instrument, frailty prevalence was compared by chi-square statistic. Cox proportional hazard models and logistic regression models were used to assess the association between frailty and mortality, hospital admissions, incident disability, and falls. Kaplan-Meier curves and log-rank test were estimated to evaluate the differences between frailty states (frail and prefrail) and robustness.

Table 4
Percentage of Different Outcomes According to the Frailty State. Comparison of Both Instruments

	Robust		Prefrail		Frail	
	FPC (n: 157)	S-FPC (n: 780)	FPC (n: 1078)	S-FPC (n: 725)	FPC (n: 401)	S-FPC (n: 131)
Age (years)	70 (68–74)	72 (69–76)*	74 (70–77)	75 (72–79)*	77 (73–81)	79 (75–83)*
Sex (% men)	64.33	47.31*	48.79	43.45	24.69	32.06
Death (%)	4.46	7.56	12.15	19.31*	26.43	34.35*
Hospitalizations (%)	12.10	16.67	20.96	26.21*	28.43	29.77
Incident disability (%)	1.27	5.26	8.81	12.97*	15.46	18.32
Falls (%)	15.29	16.67	17.44	17.38	15.46	13.74

FPC, frailty phenotype criteria; S-FPC, standardized-frailty phenotype criteria.
Data are medians (25th, 75th percentile).
*$P < .005$ S-FPC vs FPC.

Table 5
Risk of Death, Hospitalization, Incident Disability, and Falls Using Both Instruments: FPC and S-FPC

	Frailty Phenotype Criteria			Standardized-Frailty Phenotype Criteria		
	Robust	Prefrail	Frail	Robust	Prefrail	Frail
Death	HR = 1	1.63 (0.75–3.53)	3.76* (1.70–8.30)	1	1.57* (1.15–2.16)	3.26* (2.19–4.85)
Hospitalization	1	1.43 (0.90–2.27)	1.99† (1.21–3.30)	1	1.47* (1.16–1.85)	1.68† (1.14–2.47)
Incident disability	1	3.77 (0.90–15.75)	9.26* (2.16–39.69)	1	1.96* (1.30–2.97)	5.30* (2.82–9.93)
Falls	1	0.87 (0.55–1.39)	0.68 (0.39–1.19)	1	0.92 (0.69–1.23)	1.02 (0.56–1.84)

FPC, frailty phenotype criteria; HR, hazard ratio, the ratio of risk of frailty group (frail or prefrail) relative to the robust group with regards to the event of interest; S-FPC, standardized-frailty phenotype criteria.
*P value ≤ .005.
†P value ≤ .01. All analyses are adjusted by age, sex, and comorbidity.

Results

Table 2 shows the baseline characteristics of the 1645 participants included in the analysis. Of them, 729 (44.38%) were men, and median age was 74 years old (interquartile range, 70–78 years). The prevalence of frailty and prefrailty using the FPC was 24.12% and 66.4%, respectively and 6.68% and 47.81%, when we used the S-FPC ($P < .01$). When we observed the classification of individuals depending on the instrument, there were differences in 880 persons (Table 3). FPC showed a clear tendency to classify individuals in a more severe condition of frailty than S-FPC did. Among those individuals classified as robust according to S-FPC, only 20.23% (159/786) remained in the same category as FPC. In this same regard, just one-third of frail FPC individuals (32.66%; 131/401) remained in the same category when assessed using S-FPC.

During the follow-up, 244 participants (14.83%) died, 359 (21.8%) were admitted to hospitals, 274 (16.65%) suffered incident disability, and 159 (9.66%) reported at least having fallen once during the last year. When we compared the distribution of these outcomes by both frailty status and instrument, there were statistical differences depending on the instrument used between individuals classified as prefrail for death, hospitalization, and incident disability and between those classified as frail for death (Table 4). No differences were detected for individuals classified as robust for any outcome.

In this same regard, logistic regression (Table 5) showed a higher hazard ratio for prefrailty and frailty compared with robustness for death, hospitalization, and incident disability when we used S-FPC, but only for frailty when we used FPC. Neither FPC nor S-FPC found any significant difference for the risk of falling.

Because time framework is an important factor when older people are the target for prediction, we assessed the time when the difference between categories reaches clinical significance. Thus, unadjusted Kaplan-Meier curves were created for the variables where time to event was available: death and hospitalization (Figure 1). For both versions of the criteria, frailty status predicted death and hospitalization ($P < .01$). Furthermore, we analyzed the minimum time of

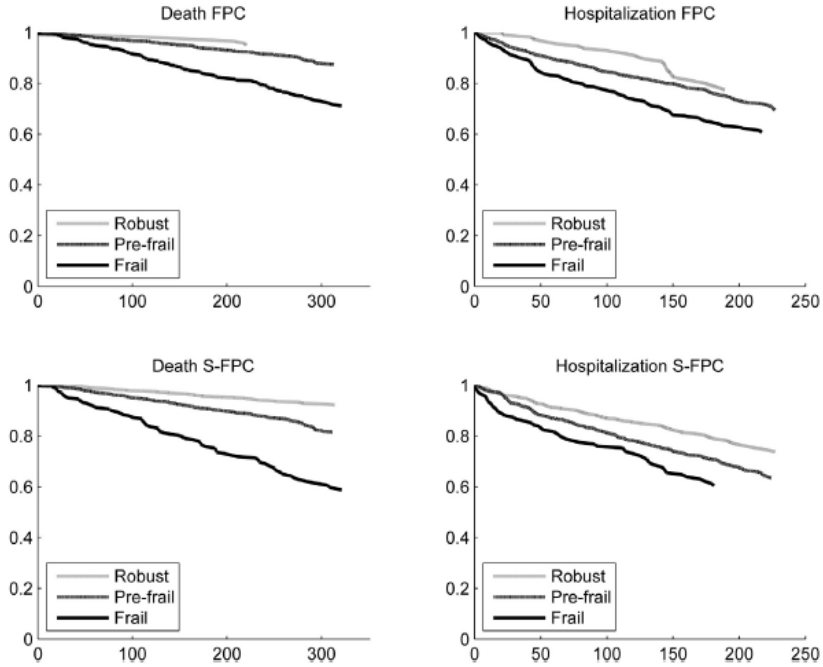

Fig. 1. Kaplan-Meier curves for death and hospitalization using FPC and S-FPC. Unadjusted model.

follow-up necessary to obtain statistically significant differences between the robust, prefrail, and frail people (Figure 2). It was noted that using S-FPC for predicting death and hospitalization for frail individuals compared with robust people, the statistical significance was reached at week 26 and week 3, respectively while at week 49 and week 24 for those classified as prefrail. On the contrary, FPC needed longer time periods: 56 and 10 weeks for frail individuals and 209 and 32 weeks for those considered prefrail.

Discussion

In this study, we show for the first time that FPC improve their predictive ability if they are standardized according to the physical characteristics of the evaluated population. This improvement embraces two main issues: First, when we used the nonstandardized instrument, the identification of prefrailty as an intermediate status is lost, mainly due to the misclassification of robust people as prefrail. When we standardized according to the phenotypic characteristics of the sample, this bias is overcome, and prefrail individuals emerge "in a consistent way, a group with an intermediate risk for adverse events between robust and frail individuals,"[1] as they were identified in the original work by Fried and colleagues. Second, the standardization makes this prediction timelier, as the hazard ratios reach statistical significance in a shorter time. This is of utmost importance when managing older people who, as one of their main characteristics, show a limited life expectancy. In these persons, prediction of events to happen in the shortest term becomes a clinical priority. As a whole, those arguments reinforce the relevance of using S-FPC as the tool of choice for detecting frailty.

The first article about physical phenotype criteria[1] was developed in the original cohort of the CHS, recruited from US communities and a second cohort of African Americans. Then, it was found that the prevalence of frailty among both subgroups was statistically different. After that, subsequent works evaluated the association between race and frailty and found ethnic disparity,[22] suggesting that the socioeconomic status, genetics, or body mass index were causes of the excess of frailty prevalence.[25] This disparity disappeared, however, when FPC were adapted to the physical characteristics of the study population.[22] This fact reinforced the differences in body composition as the responsible factor of this disparity.[22] Please note that body composition is strongly dependent on ethnicity, not just body mass index but especially in fat distribution and muscularity.[26] In consequence, great differences have been observed between races in performance-based measures, (eg, gait speed[27] and grip strength).[28] Based on this, some authors have proposed adjusting the cut-off values of these parameters to the specific characteristics of each population.[26] In the same manner, and because body composition varies systematically according to ethnic group, FPC should be applied with an ethnic-specific adaptation.[22]

From a geographical prospective, large differences have been shown in the prevalence of frailty between countries.[21] Using the phenotype model, the weighted average prevalence was 9.9% [95%

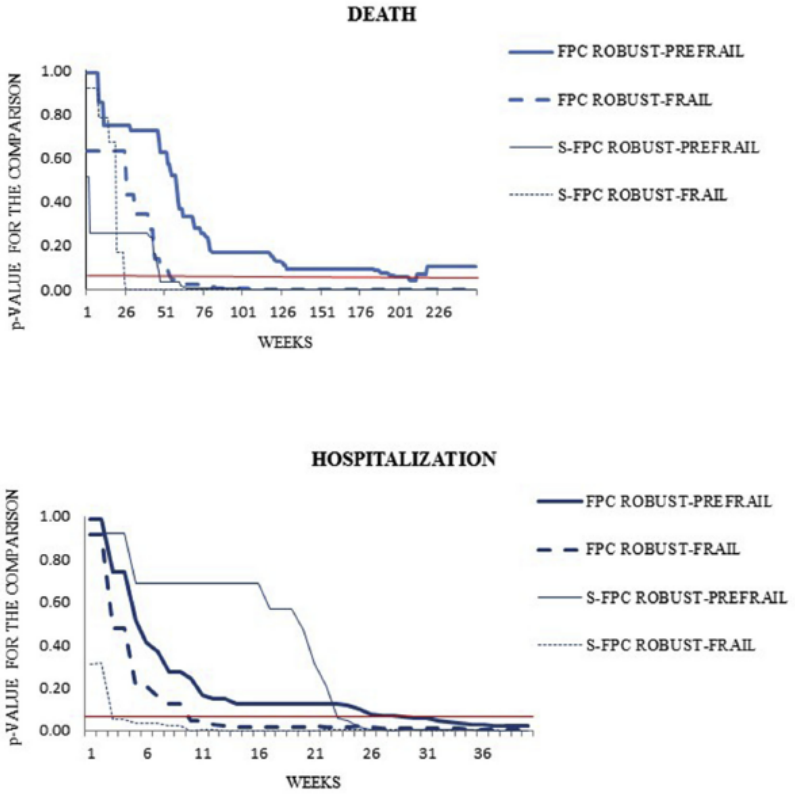

Fig. 2. Long-rank test for death and hospitalization using FPC and S-FPC. Unadjusted model.

confidence interval (CI), 9.6–10.2] for frailty and 44.2% (95% CI, 44.2–44.7) for prefrailty.[29] In some areas of Central and South America, a potentially higher prevalence was suggested for example, in Mexico,[30] Costa Rica,[31] Cuba,[32] and Peru[33] where 27.8% of the population has fulfilled the frailty criteria. In Europe, on the other hand, data from the Survey of Health, Aging, and Retirement in Europe (SHARE) showed high variations on prevalence of frailty across the European countries (tending to increase from northern to southern Europe). According to these previous data, the prevalence of frailty in Spain for the population over 65 years of age is 27.3% (23.0%–31.0%) and 50.9% (46.8%–55.1%) for prefrailty.[21] In our study, after using the original criteria, the prevalence was 24.12% for frailty and 66.4% for prefrailty (comparable to SHARE results). However, when the cut-offs were adjusted to the phenotypic characteristics of the population (S-FPC), the prevalence of frailty reduced to 6.68% and to 47.81% for prefrailty. Actually, these data are comparable to the prevalence in the north of Europe (in Sweden, frailty prevalence is 8.6%, and prefrailty prevalence is 45.3%; in Switzerland, the figures are 5.8% and 46.5%, respectively)[21] and the United States (frailty, 6.9%; prefrailty, 46.6%).[1]

Therefore, our findings are that the first longitudinal data that raise the possibility that the higher prevalence of frailty observed in ethnic minority groups using original FPC may be related in large part to ethnic differences in body composition because they disappear when frailty criteria are standardized to body composition characteristics. Thus, this higher prevalence may not represent a truly higher vulnerability to stress and functional decline.[22] In fact, there are two additional issues of interest in our findings. First, misclassification embraces a loss of discriminatory power between the categories of the frailty status that is recovered when the criteria are standardized. Second, in a tight association with the previous issue, there are substantial changes between the risks of the categories depending on the instrument used. In this regard, to be classified as prefrail does not provide any additional risk when people are classified according to the nonstandardized criteria, but they show a higher risk when the standardized ones are used. In this same regard, it must be underscored that the range of the hazard ratio for prefrail individuals regarding outcomes is larger when we used FPC instead of S-FPC, suggesting a higher heterogeneity in the conditions of the participants included in the category of prefrail in the first case.

Comparing our results with previous studies,[1] any of the tools predicted falls. These results could be justified because they are based on a question about an event (the majority of times without consequences) in the last year. The lack of awareness besides a high percentage of participants with cognitive impairment (42.95% of the total population had cognitive impairment, especially in the prefrail and frail groups) could be the cause of a report bias. In fact, just 9.66% of participants suffered at least a fall during last year, a figure lower than that reported in the literature (30% of persons over 65 years).[34]

At least two potential limitations of this study should be considered. First, gait speed was measured using a 3-meter distance instead of 15 feet as in the CHS. However, there is enough evidence supporting that there are not statistically significant differences when the distance to measure walking speed is performed using different lengths.[35] Second, physical activity was assessed using leisure activities registered on the Physical Activity Scale for the Elderly (PASE)[24] instead of the Minnesota Leisure Time Activity questionnaire used on CHS. The adjustment has been made taking into account the amount of calories used for leisure activities, thus minimizing the potential for bias. In fact, the prevalence of frailty for our cohort when the S-FPC was used was similar to that found in CHS.[1]

Conclusions

Finally, in conclusion, these findings suggest that for the characterization of older people according to their frailty status, it should be worthy to standardize the criteria to the phenotypic characteristics of the population. This suggestion is based on two main facts: (i) the risk of misclassification and, more important, (ii) the possibility of conferring wrong risks that in clinical practice would promote the use of inappropriate preventive and therapeutic measures in these persons, excluding them from the benefits of the proper management of frailty. This misclassification is especially relevant for those classified as pre-frail. Clinicians, public health professionals, policy makers, and researchers should be aware of the unadjusted tool limitations. Further research to refine the instruments and tools to assess frailty is needed, in order to improve their accuracy, their feasibility and their usefulness in the characterization of the population in different settings of care.

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