UNIVERSIDADE DE BRASÍLIA
FACULDADE DE EDUCAÇÃO FÍSICA

CINTIA RAMARI FERREIRA

DETERMINANTES MOTORES DA CAPACIDADE DE CAMINHAR EM PESSOAS COM ESCLEROSE MÚLTIPLA

BRASÍLIA
2020

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DETERMINANTES MOTORES DA CAPACIDADE DE CAMINHAR EM PESSOAS COM ESCLEROSE MÚLTIPLA

Tese de Doutorado apresentada ao
Programa de Pós-Graduação em Educação Física (PPGEF) da
Faculdadede Educação Física da Universidade de Brasília (UnB)
para a obtenção do Título de Doutora em Educação Física.

Orientadora: Professora Doutora Ana Cristina de David
Coorientador: Professor Doutor Felipe von Glehn

BRASÍLIA
2020

FICHA CATALOGRÁFICA

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Rd

Ramari Ferreira, Cintia
DETERMINANTES MOTORES DA CAPACIDADE DE CAMINHAR EM PESSOAS COM ESCLEROSE MÚLTIPLA / Cintia Ramari Ferreira; orientador Ana Cristina de David; co-orientador Felipe von Glehn. -- Brasília, 2020.
199 p.

Tese (Doutorado - Doutorado em Educação Física) -- Universidade de Brasília, 2020.

1. Esclerose Múltipla. 2. Capacidade de Caminhar. 3. Força Muscular. 4. Doenças Neurodegenerativas. 5. Fadiga. I. de David, Ana Cristina , orient. II. von Glehn, Felipe, co orient. III. Título.

Dedico esta tese de doutorado a todas as mulheres, em especial a mim.

“ Que nada nos limite, que nada nos defina, que nada nos sujeite. Que a liberdade seja nossa própria substância, já que viver é ser livre. ”

Simone de Beauvoir

Agradecimentos

Agradecer é uma forma de oração. O meu agradecimento vai muito além dos poucos nomes abaixo. Agradeço pela vida de todas as pessoas que passaram por mim nos últimos 4 anos. Agradeço ao ciclo do doutorado que se encerra, às minhas lutas e ao meu amadurecimento não só profissional, mas também pessoal.

Agradeço à minha Mãe Iraci pelo apoio incondicional aos meus sonhos sem nunca duvidar do sucesso de qualquer um deles. Agradeço ao meu Pai Geraldo por ter me ensinado tanto, em especial nos últimos anos, para entender que a vida é também aceitação. Agradeço aos meus irmãos de sangue Júlio Cesar, Carlinhos e Leandro, por estarem sempre ali me esperando pedir por socorro e por principalmente me socorrerem. Agradeço pela vida dos meus sobrinhos Helo, Lalá, Kaio, Henrique e Maria, que tornaram a caminhada dos últimos 4 anos muito mais divertida e musical.

Agradeço em especial ao Jonas, meu companheiro nos últimos 10 anos. Agradeço pela nossa amizade desde os primórdios da faculdade, pela nossa parceria e amor desde o início da minha carreira acadêmica e principalmente por ter me dado a oportunidade de morar em Brasília, onde me encontrei com o tema da minha tese de doutorado que tanto me satifaz. Obrigada Jonas, por sermos quem somos hoje e por continuar sendo um dos meus pontos de apoio na vida.

Agradeço à minha família de Brasília, amigos amados que sempre foram respiro leve, musical e de amor em todas as situações, incluindo os momentos de serem convocados para compor o grupo controle.

Agradeço aos meus companheiros de laboratório, doutorandos, mestrandos, estagiários e alunos de TCC que tanto me ensinaram e me apoiaram durante as coletas de dados e no cafezinho rotineiro.

Agradeço à minha orientadora prof. Dra. Ana Cristina de David pela paciência com a chuva de ideias semanais que inundavam minha cabeça. Por ter sido apoio e direção durante o meu doutorado para que eu conseguisse concluir este ciclo explorando as minhas capacidades, mas ao mesmo tempo sendo âncora para que eu não me perdesse durante a trajetória. Obrigada Ana, por acreditar em mim e nos nossos projetos.

Agradeço ao meu coorientador prof. Dr. Felipe von Glehn, por ter surgido em Brasília no início dos nossos projetos com esclerose múltipla. Obrigada por todo o conhecimento repassado, pelo suporte nos projetos, pelos almoços rápidos para socorrer questões urgentes dos trabalhos e por

acreditar em um trabalho multidisciplinar que tanto nos fez crescer. Agradeço também ao meu amigo neurologista Dr. Carlos Bernardo Tauil por ter colocado tanta energia nos nossos projetos e por ter me aberto janelas de oportunidades na esclerose múltipla no Brasil.

Agradeço aos professores e colegas da Faculdade de Educação Física da UnB pelos inúmeros cafezinhos, discussões e ensinamentos.

Agradeço o apoio recebido da FAPDF e da CAPES para que o meu doutorado fosse também intercionalizado. Agradeço ao prof. Dr. Ulrik Dalgas e ao seu time de pesquisadores dinamarqueses, queridos amigos e companheiros de trabalho, e principalmente ao Lars Hvid por ter sido um grande amigo apoio em parte desta trajetória.

Concluindo, agradeço a todas as pessoas diagnosticadas com esclerose múltipla que passaram pelo laboratório. Me lembro de cada sorriso de agradecimento, de cada olhar de esperança por estarem se ajudando, mas principalmente por estarem ajudando ao próximo, que também enfrenta as dificuldades da doença.

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Siglas e abreviaturas

EM	Esclerose Múltipla
SNC	Sistema Nervoso Central
MS	*Multiple Sclerosis*
CNS	*Central Nervous System*
TNF	*Tumor Necrosis Factor*
IL-1β	*Interleukin 1 beta*
IL-6	*Interleukin 6*
CIS	*Clinically Isolated Syndrome*
EMRR	Esclerose Múltipla Remitente-Recorrente
RRMS	*Relapsing-Remitting Multiple Sclerosis*
EMSP	Esclerose Múltipla Secundária Progressiva
SPMS	*Secondary Progressive Multiple Sclerosis*
EMPP	Esclerose Múltipla Primária Progressiva
PPMS	*Primary Progressive Multiple Sclerosis*
RMI	Ressonância Magnética por Imagem
EDSS	*Expanded Disability Status Scale*
MSFC	*Multiple Sclerosis Functional Composite*
T25FW	*Timed 25-Foot Walk*
MSWS-12	*Multiple Sclerosis Walking Scale – 12*
FSS	*Fatigue Severity Scale*
MFIS	*Modified Fatigue Impact Scale*
2MWT	*2-Minutes Walking Test*
6MWT	*6-Minutes Walking Test*
PSE	Percepção Subjetiva do Esforço
PDDS	*Patient Determined Disease Step*
PwMS	*Persons with Multiple Sclerosis*
RFD	*Rapid Force Development*
CI	*Confidence Interval*
TUG	*Timed Up and Go Test*
HF	*Hip Flexor*
HE	*Hip Extensor*

KE	*Knee Extensor*
KF	*Knee Flexor*
DF	*Dorsi-Flexor*
PF	*Plantar-Flexor*
COP	*Center of Pressure*
COP-vel	*COP-velocity*
COP-area	*COP-area*
DWI	*Distance Walked Index*
SDMT	*Symbol Digit Modality Test*
RPE	*Rate of Perceived Exertion*
CAPES	*Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*
HC	*Healthy Controls*
^{MS}-F	*Fatigable persons with Multiple Sclerosis*
^{MS}-NF	*Non-Fatigable persons with Multiple Sclerosis*
PWS	*Preferred Walking Speed*
FWS	*Fast Walk Speed*
WR	*Walking Reserve*

Resumo

Introdução: A esclerose múltipla (EM) é uma doença neurodegenerativa, inflamatória, crônica e desmielinizante do sistema nervoso central (SNC), e é considerada a causa principal de incapacidades em jovens adultos. As disfunções no caminhar se manifestam já no início da EM e independentemente do nível de incapacidade clínica, a capacidade de caminhar é considerada uma das funções corporais mais importantes. Além das alterações no SNC, o comprometimento de potenciais determinantes motores como da força e potência muscular, do equilíbrio estático e dinâmico e do controle motor da marcha pode contribuir para a piora na capacidade de caminhar de pessoas com EM.

Objetivos: O objetivo geral deste trabalho foi quantificar déficits na capacidade de caminhar de pessoas com EM comparado à indivíduos saudáveis sem o diagnóstico da doença e identificar os determinantes motores e a contribuição destes para o desempenho no caminhar de pessoas com EM.

Métodos: foram realizados cinco estudos a fim de responder à pergunta de pesquisa: 1) revisão sistemática sobre a contribuição da força de membros inferiores para a capacidade funcional de pessoas com EM; 2) caracterização da capacidade de caminhar, equilíbrio estático e força muscular de mulheres com EM e contribuição da força e equilíbrio para a fadigabilidade relacionada ao caminhar; 3) identificação das disfunções relacionadas à EM como a diminuição da mobilidade, da capacidade de caminhar e de funções cognitivas e comparação entre pessoas fadigáveis e não fadigáveis com EM; 4) caracterização dos déficits na potência e força de membros inferiores e da capacidade de caminhar em pessoas com EM comparadas à indivíduos controle saudáveis e investigação sobre o decréscimo na potência e força muscular induzido pela caminhada intermitente de longa duração; 5) investigação sobre os efeitos de um protocolo intermitente de caminhada de 12 minutos nos parâmetros espaço-temporais da marcha, na fadigabilidade motora relacionada ao caminhar e no estado de fadiga percebido de pessoas com EM comparados à indivíduos controle saudáveis.

Considerações finais: Foram encontrados déficits na capacidade de caminhar de pessoas com EM que variaram de 15% a 35% comparados à indivíduos controle. Aproximadamente 35% das pessoas com EM manifestaram fadigabilidade motora relacionada ao caminhar. O comprometimento dos determinantes motores de força e potência dos músculos dos membros inferios, equilíbrio semiestático e alterações nos padrões da marcha, contribuem de forma significativa para a diminuição na capacidade de caminhar de pessoas com EM.

Abstract

Introduction: Multiple sclerosis (MS) is a neurodegenerative, inflammatory, chronic and demyelinating disease of the central nervous system (CNS), and is considered the main cause of disability in young adults. Walking impairment is manifested already at the beginning of MS disease and regardless of the level of clinical disability, the ability to walk is considered one of the most important bodily function. In addition to changes in the CNS, the impairment of potential motor determinants such as muscle strength and power, static and dynamic balance and motor control of gait can contribute to the decrement in walking capacity of people with MS.

Objectives: The general objective of this doctoral thesis was to quantify deficits in walking capacity of people with MS compared to healthy controls without MS and to identify motor determinants and their contribution to walking capacity of people with MS.

Methods: five studies were carried out in order to answer the research question: 1) systematic review on the contribution of lower limb strength to the functional capacity of people with MS; 2) characterization of walking capacity, static balance and muscle strength of women with MS and the strength and balance contributions to walking-related fatigability; 3) identification of dysfunctions related to MS, such as decrement in mobility, walking capacity and cognitive functions, and comparisons between fatigable and non-fatigable people with MS; 4) characterization of the deficits in of lower limb power and strength and in walking capacity of people with MS compared to healthy controls, and investigation on the decrement in power and muscle strength induced by an intermittent walking; 5) investigation of the effects of an intermittent 12-minute walking protocol on the spatiotemporal gait parameters, walking-related fatigability and perceived fatigability of people with MS.

Final considerations: Deficits in walking capacity were found in people with MS ranging from 15% to 35% compared to healthy controls. Approximately 35% of the people with MS manifested walking-related fatigability. The impairment in motor determinants such as muscle power and strength, balance and changes in gait pattern, contributed significantly to the decrement in walking capacity of people with MS.

1. INTRODUÇÃO GERAL

1.1 Esclerose Múltipla

Esclerose múltipla (EM) é uma doença neurodegenerativa, inflamatória, crônica e desmielinizante do sistema nervoso central (SNC). Caracterizada como uma doença heterogênea, multifatorial e imunomediada, a EM é causada por uma complexa interação entre fatores genéticos e ambientais [1]. Acredita-se que a doença seja desencadeada em um indivíduo geneticamente suscetível pela combinação de um ou mais fatores ambientais como: tabagismo, estresse, condições de higiene, imunizações, infecções virais e deficiência de vitamina D. No entanto, ainda não é clara a relação causal exata entre esses fatores e o surgimento da doença [2]. A EM é a causa principal de incapacidades em jovens adultos [2]. Usualmente, o início da doença se dá entre os 20 e 40 anos de idade e tem uma alta prevalência em mulheres, embora algumas pessoas diagnosticadas com EM possam ter tido a experiência de eventos de desmielinização iniciais durante a infância ou adolescência, normalmente com a forma de EMRR [1].

Estima-se que a prevalência global de EM seja de aproximadamente 2,8 milhões de pessoas [3]. Enquanto que a EM está presente em todas as regiões do mundo, a prevalência da doença varia de acordo com a região. Na América do Norte e Europa a prevalência é de 288 e >200 pessoas diagnosticadas com a doença, respectivamente, para cada 100 mil habitantes [3]. Por outro lado, no Brasil, um estudo publicado em 2016 [4] estimou que 29467 pessoas (intervalo de confiança 95% = 25915 : 33687) são afetas pela EM, com uma prevalência que varia entre 5 e < 30 pessoas diagnosticadas por 100 mil habitantes. Especula-se que a diferença na prevalência da doença de acordo com a região geográfica global está relacionada à fatores genéticos associados, sendo os Caucasianos da região da Escandinávia e Escócia extremamente suscetíveis à doença [4]. Além disso, sugere-se que a baixa/média taxa de prevalência de EM encontrada na América Latina, comparada à América do Norte e aos países europeus, se dá pela etnia da região (em particular, ancestralidade indígena) e/ou pela diferença em fatores ambientais. Adicionalmente, uma significativa variabilidade nas condições socioeconômicas e o acesso ao sistema de saúde, que levam à um possível atraso ou não conclusão de diagnóstico, devem ser considerados como fatores potenciais para explicar estas diferenças [5].

Patologicamente, a EM é caracterizada pela presença de áreas de desmielinização (conhecidas como lesões) que são normalmente localizadas em torno de vênulas pós-capilares, tendo como característica o rompimento da barreira hematoencefálica. Os mecanismos envolvidos no rompimento da barreira hematoencefálica não são completamente

compreendidos, mas evidências sugerem os efeitos direto de citocinas pró-inflamatórias e quimiocinas tais como TNF – *Tumor Necrosis Factor* (fatores de necrose tumoral), IL-1β - *Interleukin 1 beta* (Interleucina 1 beta) e IL-6 – *Interleukin 6* (Interleucina 6). A desregulação da barreira hematoencefálica aumenta a migração transendotelial de leucócitos, incluindo macrófagos, células T e células B para o SNC, tendo como consequências o aumento da inflamação, perda de oligodendrócitos, gliose reativa (alteração da substância branca) e degeneração neuroaxonal. As lesões podem ocorrer tanto na substância branca quanto na substância cinzenta do encéfalo e podem ser encontradas em todo o SNC, incluindo o nervo óptico e medula espinal [1]. A bainha de mielina, estrutura que envolve e isola as fibras nervosas com importante função na transmissão do impulso nervoso, é degenerada e a velocidade de propagação do impulso nervoso diminui ocorrendo adicionalmente perdas neuronais [6].

As manifestações clínicas e o curso da EM são heterogêneos. Na maioria das pessoas diagnosticadas com a doença, ataques reversíveis com déficit neurológico – conhecidos como ataques ou recaídas, normalmente tem duração de alguns dias e caracterizam a fase inicial da doença, ou seja, a síndrome clínica isolada (*CIS – clinically isolated syndrome*) e a EM remitente-recorrente (EMRR) (*RRMS – relapsing-remitting multiple sclerosis*)[1]. Ao longo do tempo, o desenvolvimento de déficits neurológicos permanentes e a progressão das deficiências clínicas se tornam proeminentes, caracterizando a EM secundária progressiva (EMSP) (*SPMS – secondary progressive multiple sclerosis*). A minoria dos pacientes apresenta o curso progressivo da doença desde o início, o qual é conhecido como EM primária progressiva (EMPP) (*PPMS – primary progressive multiple sclerosis*). Cada subtipo da EM pode ser classificado como ativo ou não ativo de acordo com as avaliações clínicas sobre a ocorrência de recaídas ou atividade das lesões, estas detectadas por meio da ressonância magnética por imagem (RMI). Além disso, pacientes com EMPP ou EMSP podem ser classificados de acordo com a progressão das incapacidades ocorridas em um dado período de tempo [1,7] A figura 1 apresenta o curso clínico da EM de acordo com os subtipos da doença.

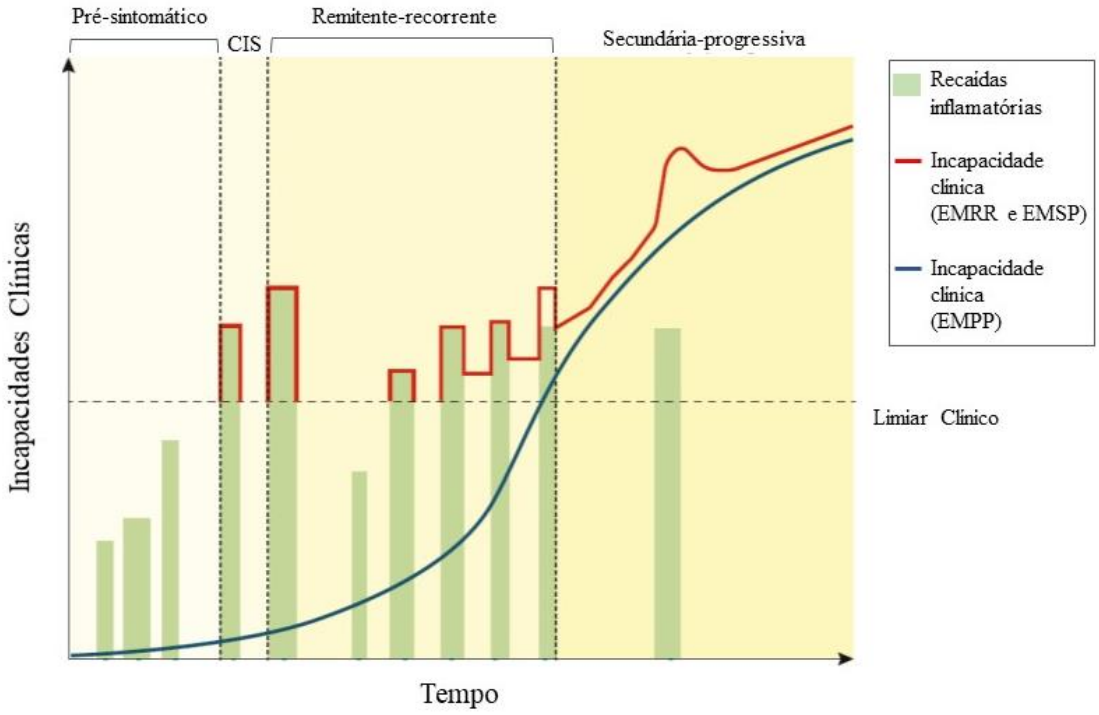

Figura 1: Curso clínico da esclerose múltipla (figura adaptada de Filippi et al. 2019). EMRR, esclerose múltipla remitente-recorrente. EMSP, esclerose múltipla secundária progressiva. EMPP, esclerose múltipla primária progressiva. CIS, síndrome clínica isolada (clinically isolated syndrome).

A EM é uma doença que apresenta uma variedade de sintomas. A maioria das pessoas diagnosticas com EM percebem e reportam ao menos algum grau de disfunção e incapacidade imediatamente após o início da doença. Sintomas sensoriais e fadiga são particularmente presentes em todos os estágios da doença, sendo que 85% dos pacientes reportam algum sintoma sensorial e 81% relatam sobre fadiga. Além disso, aproximadamente 50% dos pacientes apresentam disfunções cognitivas que variam de mínima a moderada no primeiro ano de diagnóstico. Com relação à mobilidade, no primeiro ano da doença ao menos 35% dos pacientes são notavelmente afetados, e, adicionalmente, 15% destes necessitam de suporte para caminhar [8].

1.2 Capacidade de caminhar na EM

De uma perspectiva evolutiva, caminhar é uma forma essencial de locomoção em humanos. No entanto, o caminhar não é considerado obrigatório para a sobrevivência [9], mas desempenha um papel significativo para a preservação da independência pessoal e manutenção da qualidade de vida [10]. O início e o ajuste fino da caminhada dependem da ativação de

neurônios situados em diferentes regiões do cérebro, incluindo os núcleos da base, córtex motor, cerebelo e núcleos do tronco encefálico. Além disso, a regulação supraespinal do caminhar compreende a ativação dos sistemas locomotores medulares, o ajuste para o início do caminhar, o controle da velocidade geral, o refinamento do padrão motor em resposta ao feedback dos membros e a orientação do movimento dos membros [11]. Como a capacidade de caminhar requer energia e controle do movimento, vários sistemas do organismo são envolvidos na tarefa e fornecem suporte para o melhor desempenho da mesma. Assim, a desaceleração na velocidade de caminhar pode refletir danos presentes no SNC e/ou no sistema musculoesquelético [9]. Na EM, portanto, o comprometimento do caminhar é um potencial protagonista para a identificação de disfunções no SNC.

As disfunções no caminhar se manifestam já no início da EM e estão presentes em pessoas com baixo grau de incapacidade, piorando de acordo com a progressão da doença [12]. Independentemente do nível de incapacidade clínica, na EM, a capacidade de caminhar é considerada uma das funções corporais mais importantes tanto do ponto de vista do paciente quanto dos neurologistas [13]. Além disso, o comprometimento do caminhar é o segundo indicador mais forte de autoavaliação da saúde (por exemplo, utilizando um questionário de cinco pontos validado e adotado pela Organização Mundial de Saúde) em pessoas com EM [14]. Na EM, a capacidade de caminhar é um marcador importante da progressão da doença [15]. Ao aplicar a escala expandida do estado de incapacidade (*expanded disability status scale*, EDSS), que quantifica as incapacidades ocorridas durante a evolução da EM ao longo do tempo, pontuações que variam entre 4.0 e 7.5 são primariamente baseadas na distância percorrida (<500 metros) pelo paciente [7]. Além disso, o composto funcional de EM (*multiple sclerosis functional composite*, MSFC), utilizado para mensurar a gravidade da doença principalmente em pesquisas clínicas, incorpora o teste de 25 pés de caminhada (*Timed 25-Foot Walk*, T25FW) como medida para a velocidade de caminhar [16]. Nesta população, as disfunções no caminhar vêm acompanhada de déficits na capacidade de manter o controle motor, que geram anormalidades de certas fases e parâmetros da marcha [17]. À medida que a disfunção no caminhar aumenta e a velocidade máxima começa a deteriorar, ocorre uma mudança no grau de impacto da capacidade de caminhar na vida diária de pessoas diagnosticadas com EM [10]. Especificamente, níveis mais baixos de desempenho, ou seja, executar o T25FW em mais de 8 segundos, tem sido associado ao desemprego, necessidade de assistência médica frequente, divórcio, suporte para caminhar e ser incapaz de realizar atividades da vida diária, como limpeza, compras de supermercado e cozinhar [10]. Neste contexto, a caminhada torna-se muito

limitada na vida diária de pessoas com EM quando a velocidade máxima atinge entre 0,70 a 0,95 metros por segundo (m/s) [10,18].

A capacidade de caminhar pode ser definida como o desempenho obtido em uma determinada tarefa de caminhada, sendo a velocidade e a distância percorrida (por exemplo, em um teste de caminhada de média e longa distância) parâmetros válidos para a avaliação do desempenho [19]. Além disso, há também a percepção da capacidade de caminhar, que pontua limitações no caminhar na vida cotidiana de pessoas com EM, baseada em escalas autorreportadas que mensuram o impacto da EM na caminhada (*multiple sclerosis walking scale – 12*, MSWS-12). Desta forma, a capacidade de caminhar na EM pode ser avaliada de forma objetiva, por meio de testes de caminhada, e de forma subjetiva autorreportada [19,20]. No entanto, a capacidade para caminhar média e longa distâncias pode estar relacionada não somente às incapacidades adquiridas pelo paciente com a evolução da doença, mas também aos sintomas de fadiga [21].

1.3 Sintomas de fadiga e a capacidade de caminhar na EM

Os sintomas de fadiga são altamente relatados e estão presente em cerca de 70% das pessoas diagnosticadas com EM[21]. A fadiga na EM pode ser entendida como "traço de fadiga" ou "estado de fadiga". Traço de fadiga compreende a fadiga patológica referente a uma sensação frequente, prolongada ou constante durante longos intervalos de tempo, que representa o construto de fadiga avaliado por questionários de autorrelato [22,23]. A escala de gravidade da fadiga (*fatigue severity scale*, FSS) é uma escala de 9 itens que mede a gravidade da fadiga e seu efeito nas atividades e estilo de vida de uma pessoa com uma variedade de distúrbios [24]. A FSS foi originalmente criada para pessoas com EM e é uma das escalas mais utilizadas para verificar a associação entre fadiga e capacidade de caminhar na EM. A maioria dos estudos relatam associações não significativas entre a FSS e a capacidade de caminhar na EM [25–27]. Outro questionário autorreferido muito utilizado na EM é a escala modificada do impacto da fadiga (*modified fatigue impact scale*, MFIS), que além de oferecer uma pontuação única total, diferencia a percepção do impacto da fadiga em subdomínios relacionados às funções físicas, cognitivas e psicossociais. A velocidade de caminhada e a distância percorrida em testes de média e longa distâncias correlacionam-se de forma similar com a pontuação total da MFIS [21,28,29], embora a maioria das associações não sejam estatisticamente significativas. Com relação ao subdomínio físico da MFIS, estudos apontam associações significativas com a distância percorrida nos testes de dois minutos de caminhada (*2-minutes walking test*, 2MWT) e de seis minutos de caminhada (*6-minutes walking test*, 6MWT) [21,28–30]. Além disso, o

impacto da fadiga total (MFIS total) e o subdomínio físico (MFIS físico) explicam 24% e 40% da variância na capacidade de caminhar autorreportada mensurada pela MSWS-12, respectivamente [21]. No geral, as evidências apontam que a percepção subjetiva geral do impacto da fadiga (MFIS total) não se associa significativamente com a capacidade de caminhar, mas sim com a caminhada autorreportada. No entanto, o subdomínio físico da MFIS aponta associações significativas com médias e longas distâncias percorridas e com a MSWS-12, sugerindo que a MFIS físico é melhor sugerida para avaliar o impacto do sintoma de fadiga na capacidade de caminhar em pessoas com EM.

No que se refere ao estado de fadiga, este é definido como as sensações transitórias de cansaço ou falta de energia durante ou logo após uma determinada tarefa, descritas como fadiga por atividade ou fadigabilidade. A fadigabilidade, portanto, tem um componente percebido ou subjetivo (percepção subjetiva do esforço, PSE) e um componente de desempenho (objetivo) [23]. A fadigabilidade percebida após o 6MWT tem sido fortemente associada à capacidade de caminhar (coeficiente de correlação = -0,71) [22], porém valores arbitrários de PSE mas não o incremento ao longo do tempo, mensurados pela escala de Borg, são correlacionados com a distância percorrida [31]. A fadigabilidade objetiva medida durante uma tarefa motora (ou seja, fadigabilidade motora) pode ser avaliada pelo desempenho motor de contrações musculares isoladas, calculado pelo declínio da força durante ou após contrações estáticas e/ou dinâmicas [32]. A fadigabilidade durante contrações dinâmicas do joelho tem sido fortemente associada com a capacidade de caminhar e com a caminhada autorreportada em pessoas com EM, explicando significativamente 9% e 16% da variância no 6MWT e na MSWS-12, respectivamente [33]. Parece evidente que a fadigabilidade motora relacionada ao caminhar está associada à distância percorrida em testes de média e longa duração [23], porém não há evidências de como a fadigabilidade no caminhar está associada à velocidade basal de caminhada em pessoas com EM. Concluindo sobre a fadigabilidade e a capacidade de caminhar na EM, durante o exercício, sugere-se que a ativação central para os músculos diminui em pacientes fatigados, e a diferença entre pacientes com EM que apresentam sintomas de fatiga comparados aos que não apresentam sintomas de fatiga pode aumentar ao longo do exercício [26]. Além disso, a associação entre a capacidade de caminhar e o comprometimento da ativação central para os músculos tem sido reportada em pessoas com EM [34].

1.4 *Framework*: problema de pesquisa

Apesar do comprometimento da capacidade de caminhar ser consideravelmente impactante em pessoas com EM, apenas algumas opções farmacológicas (por exemplo,

Fampridina) estão disponíveis para uma fração dos pacientes [35,36]. Felizmente, uma ampla gama de intervenções não farmacológicas existe e tem sido sugerida para melhorar a capacidade de caminhar na EM, sendo as intervenções mais promissoras as de exercícios físicos (exercícios gerais, treinamento aeróbio, treinamento resistido, ioga e pilates) [37], fisioterapia [38], órteses e estimulação elétrica funcional [39], treino de marcha com auxílio de robótica [40], vibração corporal [41] e realidade virtual [42]. Embora as intervenções não farmacológicas com o objetivo de melhorar a capacidade de caminhar, em alguns casos, tenham se mostrado eficazes, é possível que existam determinantes não identificados, e mesmo que conhecidos, entender o quanto estes determinantes explicam o desempenho no caminhar ainda se faz necessário na EM.

Com relação aos determinantes, a figura 2 apresenta de forma resumida um modelo dos potenciais determinantes que possam contribuir para as alterações no caminhar de pessoas com EM ao longo do curso da doença. Considerando a fisiopatologia da EM, a doença é caracterizada por alterações no SNC e dentre os potenciais determinantes da capacidade de caminhar estão a inflamação, número e extensão das lesões no SNC, velocidade de condução do impulso nervoso e atrofia cerebral. Além das alterações centrais, disfunções motoras ocorrem em pessoas com EM e podem refletir o impacto da doença no SNC, assim como a modificação e melhora destas disfunções podem contribuir para que as alterações no SNC ocorram de forma gradativa e menos agressiva [37]. Assim, as disfunções na EM caracterizam os potenciais determinantes motores que contribuem para a capacidade de caminhar, dentre eles: força e potência muscular, equilíbrio estático e dinâmico e o padrão da marcha como as alterações dos parâmetros espaço-temporais. As contribuições dos determinantes do SNC e motores podem ser identificadas por meio do nível de capacidade funcional. No entanto, é importante salientar que existe uma gama de fatores e possíveis determinantes que não estão inseridos no modelo da figura 2, como as funções cognitivas, sintomas de depressão e traço de fadiga, dentre outros que impactam o caminhar na EM.

Figura 2: Potencias determinantes do sistema nervoso central (SNC) e motores que contribuem com a capacidade de caminhar em pessoas com esclerose múltipla, e, consequentemente com os resultados clínicos. Estes classificado de acordo com a EDSS (expanded disability status scale), PDDS (patient determined disease step) e MSFC (multiple sclerosis functional composite). 2MWT, 2-minute walking test (teste de 2 minutos de caminhada); 6MWT, 6-minute walking test (teste de 6 minutos de caminhada).

A quantificação do déficit existente na capacidade de caminhar de pessoas com EM e a identificação de potenciais determinantes do caminhar podem abrir caminhos para novas intervenções e além disso, auxiliar no refinamento e expansão de abordagens farmacológicas e não farmacológicas com foco na melhoria da capacidade de caminhar em pessoas com EM.

Tendo em vista que a capacidade de caminhar na EM é considerada um marcador importante de progressão das incapacidades clínicas da doença, a figura 3 apresenta um modelo para ilustrar a pergunta de pesquisa a ser elucidada neste trabalho. Na figura 3 estão presentes as curvas da capacidade de caminhar ao longo da vida considerando os valores de referência de sujeitos saudáveis sem o diagnóstico de EM e de pessoas com EM. Além disso, a figura 3 apresenta a hipótese do déficit no desempenho em testes de caminhada e na fadigabilidade no caminhar em pessoas com EM comparados à sujeitos saudáveis. Os determinantes motores de força e potência muscular, equilíbrio estático e dinâmico e as alterações no padrão da marcha,

estão posicionados abaixo da curva da capacidade caminhar de forma a ilustrar a contribuição destes para o desempenho no caminhar. Já as incapacidades clínicas (apresentadas abaixo da curva), que classificam os pacientes quanto ao nível da doença, são baseadas pelas pontuações nas escalas do estado de incapacidade e de autodeterminação do nível da doença de acordo com a capacidade de caminhar. Contudo, a pergunta de pesquisa a ser desenvolvida neste trabalho é: existe déficit na capacidade de caminhar de pessoas com EM comparadas à sujeitos saudáveis sem a doença, e, quais os determinantes motores e a contribuição destes para o desempenho do caminhar na EM?

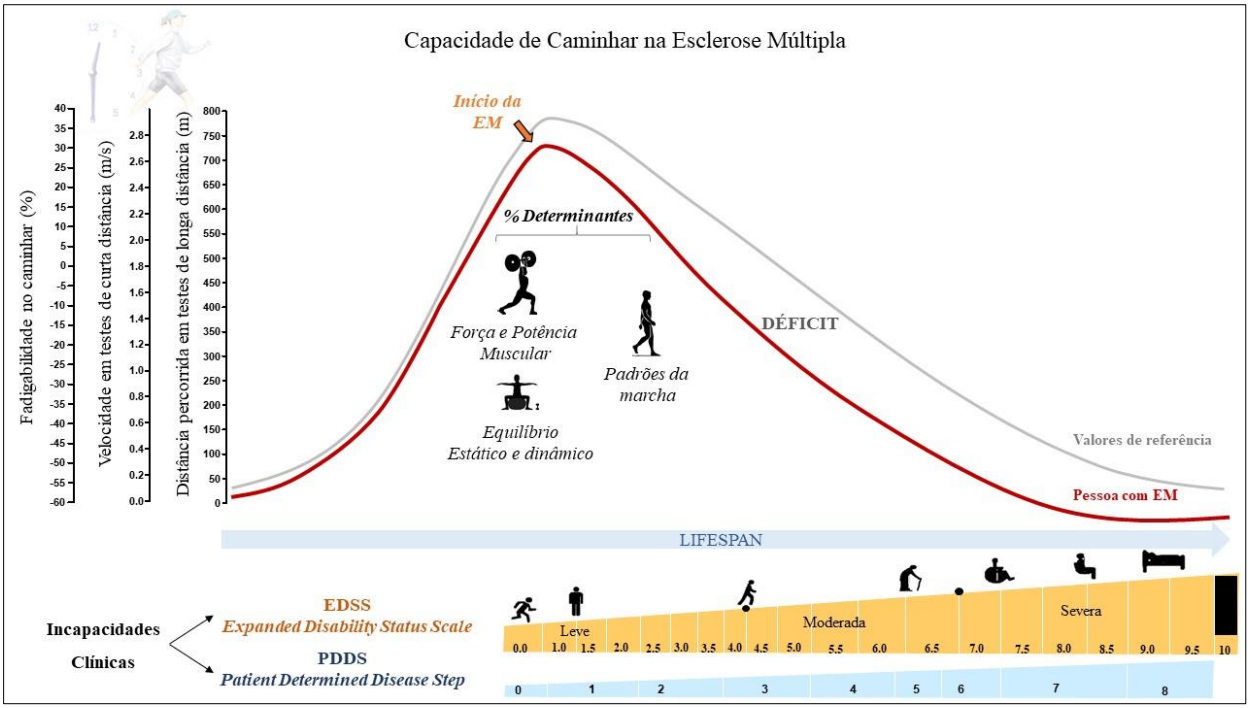

Figura 3: Framework. *Ilustração da pergunta de pesquisa.*

2. OBJETIVOS

2.1 Objetivo Geral

O objetivo geral deste trabalho é quantificar déficits na capacidade de caminhar de pessoas com EM comparado à indivíduos saudáveis sem o diagnóstico da doença e identificar os determinantes motores e a contribuição destes para o desempenho no caminhar de pessoas com EM.

2.2 Objetivos Específicos

Artigo 1: Revisão sistemática com o objetivo de compreender a importância da força dos músculos dos membros inferiores para a capacidade funcional de pessoas com EM. O trabalho busca identificar estudos que mensuraram a força de membros inferiores e a capacidade

funcional de pessoas com EM, além de propor um mapa de acordo com as associações existentes entre grupos musculares específicos e os resultados de testes de capacidade funcional em pessoas com EM.

Artigo 2: Estudo transversal que tem por objetivo caracterizar a capacidade de caminhar, equilíbrio estático e força muscular de mulheres com curso leve de EMRR. Adicionalmente, o estudo busca investigar a fadigabilidade relacionada à marcha durante o teste de seis minutos de caminhada – 6MWT e as possíveis associações com a força muscular e equilíbrio.

Artigo 3: Estudo transversal que busca identificar as disfunções relacionadas à EM como a diminuição da mobilidade, da capacidade de caminhar e de funções cognitivas. Além disso, comparar as disfunções entre pessoas com EM que apresentam e que não apresentam fadigabilidade motora relacionada ao caminhar, controlando por características clínicas da EM e demográficas.

Artigo 4: Estudo transversal que tem por objetivos (1) investigar e caracterizar déficits na potência e força de membros inferiores mensurados por meio da plataforma de força, assim como, déficit na capacidade de caminhar em pessoas com EM comparadas à indivíduos controle saudáveis; (2) comparar os déficits motores entre pessoas com EM que apresentam e que não apresentam fadigabilidade motora relacionada ao caminhar, e, entre os pacientes com baixa e moderada disfunções no caminhar; (3) verificar as associações da potência e força muscular com a capacidade de caminhar, nível de incapacidade da doença e traço de fadiga; (4) investigar se há decréscimo na potência e força muscular de membros inferiores induzido por um protocolo de caminhada e a contribuição deste para a fadigabilidade motora relacionada ao caminhar.

Artigo 5: Estudo transversal que busca verificar os efeitos de um protocolo intermitente de caminhada de 12 minutos nos parâmetros espaço-temporais da marcha, na fadigabilidade motora relacionada ao caminhar e no estado de fadiga percebido de pessoas com EM comparados à indivíduos controle saudáveis. Adicionalmente, o trabalho tem por objetivo verificar a associação das mudanças nas variáveis espaço-temporais da marcha com a fadigabilidade motora relacionada ao caminhar, fadigabilidade percebida, traço de fadiga, cognição e o grau do estado da doença.

3. ESTUDOS

3.1 Artigo 1 – Publicado

Systematic Review

THE IMPORTANCE OF LOWER-EXTREMITY MUSCLE STRENGTH FOR LOWER-LIMB FUNCTIONAL CAPACITY IN MULTIPLE SCLEROSIS: SYSTEMATIC REVIEW

Cintia Ramari [1], Lars G. Hvid [2], Ana Cristina de David [1], Ulrik Dalgas [2]

[1] Faculty of Physical Education, University of Brasilia, Brasília, Brazil

[2] Section for Sport Science, Department of Public Health, Aarhus University, Aarhus, Denmark

Revista: ANNALS OF PHYSICAL AND REHABILITATION MEDICINE

Fator de Impacto: 3.65

https://doi.org/10.1016/j.rehab.2019.11.005

ARTICLE HISTORY:

Received 14 June 2019

Accepted 11 November 2019

Abstract

Background. Lower-limb functional capacity is impaired in most persons with multiple sclerosis (PwMS). Reductions in lower-extremity muscle mechanical function (e.g., muscle strength) appear to have critical implications for lower-limb functional capacity. However, no review has summarized the current knowledge about the importance of muscle strength for functional tasks in PwMS. Expanding the current knowledge would advance the design of both clinical and research interventions aiming to improve functional capacity in PwMS.

Objectives. 1) to identify studies that measured lower-extremity muscle mechanical function and lower-limb functional capacity outcomes in PwMS, and 2) to map associations between muscle strength and functional capacity.

Methods. This review was based on a literature search (databases: PubMed, Embase). Included studies had to report data on lower-extremity muscle mechanical function and lower-limb functional capacity outcomes in PwMS. The associations between muscle strength and functional capacity were analyzed by using the reported correlation coefficients (R) recalculated to the determination coefficient R^2. Randomized trials and observational studies were included.

Results. A total of 59 articles were reviewed; 17 (773 participants) reported associations between muscle strength and functional capacity. Lower-extremity muscle mechanical function explained a significant part of the variance in most lower-limb functional capacity tests (approximately 20-30%). This was particularly evident in muscle strength from the weakest leg. Muscle strength was predominantly tested on knee extensors and knee flexors by using isokinetic dynamometry during maximal isometric (0°/sec) and dynamic (30-60°/sec) contractions. Walking tests such as the timed 25-foot walk test and 10-min, 2-min and 6-min walk test were the most frequently performed functional capacity tests.

Conclusions. In PwMS, muscle strength of particularly the weakest limb explains 20% to 30% of the variance across a number of lower-limb functional capacity tests. Thus, exercise programs should focus on increasing lower-extremity muscle mechanical function in PwMS and minimizing strength asymmetry between limbs.

Keywords: multiple sclerosis; lower extremity; muscle mechanical function; functional capacity; walking capacity.

Introduction

Lower-limb functional capacity is impaired in most people with multiple sclerosis (PwMS), as exemplified by the high prevalence of walking impairments in MS, with up to 68% of individuals experiencing some degree of ambulatory dysfunction [1,2]. Moreover, PwMS with both an early and long-term diagnosis perceive walking as their most important bodily function [3,4]. Such findings emphasize the importance of maintaining lower-limb functional capacity at the highest possible level in PwMS. As such, it seems essential to identify modifiable determinants of lower-limb functional capacity and then develop interventions targeting these.

Among several identified determinants of lower-limb functional capacity, including balance and cardiorespiratory capacity [5,6], muscular strength clearly stands out. Reductions in muscle mechanical function, comprising isometric strength, dynamic strength, “explosive” strength (rapid force development [RFD]), and power [7], appear to have critical implications in PwMS [8] on all levels of the International Classification of Functioning, Disability and Health model including activity level [9]. The lower extremity is of particular importance because in MS, much larger muscle strength deficits are seen in the lower than upper extremity [8]. Some studies show that reduced lower-extremity muscle strength of particularly

the weaker leg [10] negatively affects walking performance [10–13], balance [12,14,15], stair climbing and sit-to stand ability [10,13,16,17]. This situation is likely related to the lower physical activity levels often observed in PwMS as compared with healthy controls [17]. Because reduced muscle strength is associated with increased risk of all-cause mortality [18], cardiovascular disease, metabolic syndrome, osteoporosis and some forms of cancer in the general population [19–21], such health-related risks are also likely increased in PwMS. However, we lack reviews evaluating the association of muscle strength in lower-extremity muscle groups with lower-limb functional capacity in PwMS. Such knowledge would advance our general understanding of the importance of lower-extremity muscle strength in PwMS and potentially also help guide the design of effective exercise interventions aimed at improving lower-limb functional capacity in PwMS.

Hence, to expand our understanding of the importance of muscle strength for functional capacity in PwMS, we performed a systematic literature review to 1) identify studies that measured lower-extremity muscle mechanical function and lower-limb functional capacity in PwMS, and 2) map existing associations between lower-extremity muscle mechanical function and lower-limb functional capacity in PwMS to allow for extracting relevant association patterns.

Methods

Study selection

The present review focused on English-language studies examining lower-extremity muscle mechanical function and lower-limb functional capacity in PwMS. The review was based on a literature search of 2 databases (PubMed, Embase) to retrieve cross-sectional and intervention studies published before February 2019. Review articles were not included. An independent search methodology aiming to identify relevant studies reporting data on muscle strength and

functional tasks in MS was applied. The MeSH search terms included “Muscle Strength” AND [“Exercise Test” OR “Walk Test] AND “Multiple Sclerosis”. Single-case and case reports (n<5) were excluded. We also excluded studies with no methodological description of the relevant measurements, that applied subjective muscle strength evaluations (e.g., scales), and with no data on muscle strength or functional tasks.

Muscle mechanical function and functional capacity outcomes

Muscle mechanical function outcomes from the identified studies were reviewed, and data extraction included data on the involved lower-extremity muscle group(s), the type and velocity of the muscle contraction(s), and whether it was the strongest or weakest lower limb (or most/least affected) that was used when performing the strength test(s). In addition, the type of device(s) used to assess muscle strength and the unit(s) used to report muscle strength were recorded.

Concerning functional capacity involving the lower limbs, the outcomes were reviewed according to the tests performed to evaluate mobility, balance, lower-limb strength, and short walking capacity (e.g., the timed 25-foot walk test [T25FWT]) and long walking capacity (e.g., the 6-min walk test [6MWT]). Also, data describing a potential association between lower-extremity muscle mechanical function and lower-limb functional capacity were extracted. Additional tests that were reported in the studies and related to the lower-limb capacity were reviewed, including those based on subjective scales.

Data analysis

The recorded associations between lower-extremity muscle mechanical function and lower-limb functional capacity were analysed by using the reported correlation coefficients (R). The R coefficients were squared if not already done and reported as R^2 values. To map the

associations, when the study performed more than one evaluation using the same method to assess muscle mechanical function, mean and 95% confidence intervals (CIs) of R^2 values were calculated. The included studies reported different sample sizes and sex ratio, which could be considered confounding factors when evaluating the association between strength and functional outcomes. Therefore, when determining the overall pattern across existing studies on the association for each lower-extremity muscle group, mean and 95% CIs of R^2 values were weighted by sample size and sex ratio (women/men) from each study. Because most of the studies evaluated knee extensor and flexor muscle strength, we could use these outcomes to report the R^2 values according to the type of contraction (isometric or dynamic). All data analyses were conducted with SPSS 25.0 (SPSS Inc.).

Results

Study selection

The selection of studies is in Figure 1. We found 123 and 98 articles in PubMed and EMBASE, respectively. After removing 32 duplicates, 189 articles were screened by the abstracts and 99 articles were excluded. Finally, 59 articles were included in the review and their description is in Table 1 along with the methods applied for assessment of lower-extremity muscle mechanical function and lower-limb functional capacity.

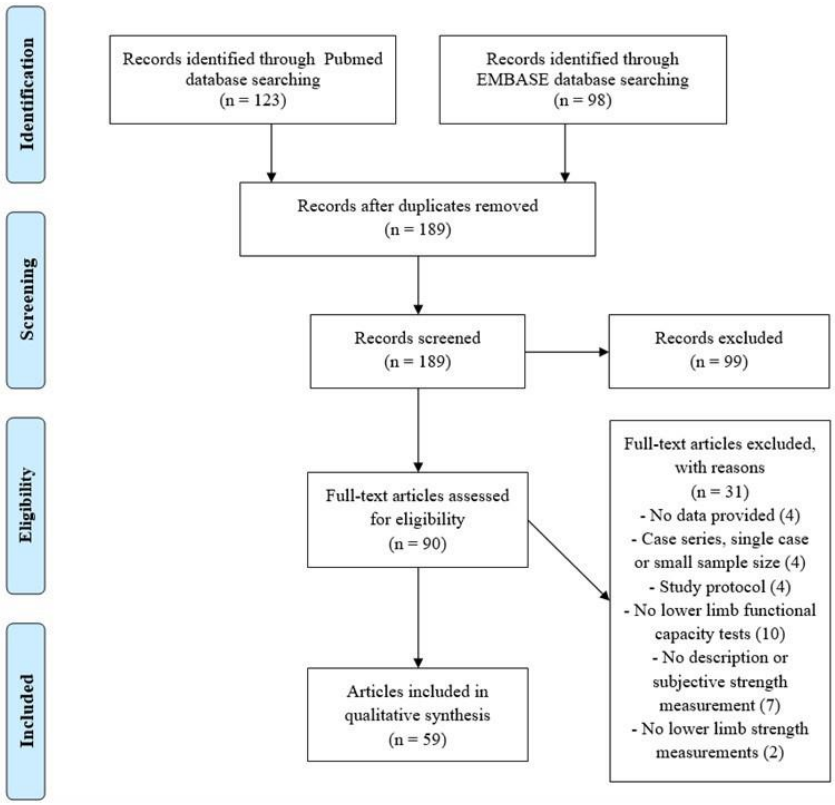

Figure 1. Flowchart of search results and study selection for the review.

Most studies (see table 1, supp.) had a sample size of 20 to 60 participants regardless of study type (cross-sectional or intervention), although the articles from Callesen et al. [14] and Thoumie et al. [12] had sample sizes of 90 and 100 participants, respectively. The mean age was 30 to 50 years, with a higher prevalence of women. Most studies reported expanded disability status scale (EDSS) scores to classify the level of disability (general inclusion criteria ≤ 6.5), with the range of mean values of 2.8 to 6.5. Regarding lower-extremity muscle mechanical function, the most commonly used device was the isokinetic dynamometer followed by the handheld dynamometer. The muscle mechanical function of several muscle groups was evaluated with the knee extensor and flexor muscles most frequently. Lower-limb functional capacity tests were applied, predominantly focused on walking ability, with the T25FWT and the 6-min walk test (6MWT) the most frequent choices when evaluating short and long walking distance, respectively. Furthermore, a large number of studies evaluated gait parameters including velocity by an instrumented walkway or other gait analysis devices

[6,12,13,22–26]. To evaluate mobility and dynamic balance, the Timed Up and Go test (TUG) was the most-used test, whereas the sit-to-stand test was the most-used test to provide a proxy measure of lower-extremity muscle strength. To evaluate balance alone, the most-used functional test was the Berg balance scale.

Table 2 summarises data from 17 articles reporting on the association between lower-extremity muscle mechanical function and the most frequently performed lower-limb functional capacity tests. Because most studies provided results on maximal isometric or dynamic muscle strength but only few on "explosive" muscle strength (RFD), associations with the latter outcome were excluded from the overall analysis. Most studies focused on the knee extensor and/or the knee flexor muscles, but studies from Almuklass et al. [27], Callesen et al. [14], Ng et al. [28] and Wagner et al. [29] also evaluated muscle strength of plantar flexor and/or dorsal flexor muscles; the study from Møller et al. [30] evaluated muscle strength of the hip extensor and hip flexor muscles. Mañago et al. [15] performed the most comprehensive evaluation of the association between lower-extremity muscle strength and lower-limb functional capacity: in addition to knee flexion and extension, this study also included hip extension, flexion, abduction, and adduction and ankle plantar flexion as well as trunk flexion. A large number of studies examined both the weakest (≈ most affected) and the strongest (≈ least affected) leg. Finally, most studies reported isometric muscle strength and/or slow dynamic muscle strength (30-60°/sec).

Table 2. Articles reporting data on the association between lower-limb strength and functional capacity.

Authors	Limb: muscle group, velocity (position), unit	Short walking test	Long walking test	TUG	Sit-to-Stand
Almuklass et al. [27]	Weakest (W) | Strongest (S): PF, 0º/s, Nm DF, 0º/s, Nm	W | S: **0.11** | 0.02 **0.25** | **0.11**	W | S: 0.04 | 0.00 **0.18** | 0.04		
Bowser et al. [16]	Both: 1RM leg press				0.10

Broekmans et al. [32]	Weakest (W) | Strongest (S):	W | S:	W | S:	W | S:	
	KE, 0º/s (45º), Nm	**0.09** | **0.07**	**0.26** | **0.15**	**0.12** | **0.07**	
	KE, 0º/s (90º), Nm	**0.12** | **0.18**	**0.29** | **0.28**	**0.12** | **0.16**	
	KE, 60º/s, Nm	**0.13** | **0.16**	**0.30** | **0.26**	**0.11** | **0.12**	
	KF, 0º/s (45º), Nm	**0.27** | **0.12**	**0.44** | **0.21**	**0.28** | **0.10**	
	KF, 0º/s (90º), Nm	**0.37** | **0.28**	**0.53** | **0.28**	**0.32** | **0.30**	
Callesen et al. [14]	Weakest (W):	W:	W:		
	KE, 0º/s (70º), Nm	**0.22**	**0.18**		
	KF, 0º/s (30º), Nm	**0.19**	**0.14**		
	PF, 0º/s, Nm	**0.19**	**0.21**		
	DF, 0º/s, Nm	**0.12**	**0.16**		
Güner et al. [23]	Weakest (W) | Strongest (S):	W | S:			
	KE, 60º/s, Nm	**0.40** | **0.34**			
	KF, 60º/s, Nm	**0.33** | **0.22**			
Hameau et al. [57]	Weakest (W):	W:	W:	W:	
	KE, 0º/s (90º), Nm	**0.31**	**0.17**	**0.24**	
	KF, 0º/s (90º), Nm	**0.21**	**0.16**	0.11	
Jensen et al. [60]	Weakest (W) | Strongest (S):	W | S:			W | S:
	KE, 30º/s, Nm	**0.09** |			
	KE, Composite, Nm	**0.25** |			
	KE, 0º/s, RFD (Nm/s)	|			| **0.25**
	KF, 0º/s, RFD (Nm/s)	**0.25**			**0.25** |
		0.25 |			
Kjølhede et al. [10]	Weakest (W) | Strongest (S):	W | S:	W | S:		W | S:
	KE, 0º/s (70º), Nm/Kg	**0.23** | **0.16**	**0.30** | **0.14**		**0.12** | 0.05
	KF, 0º/s (20º), Nm/Kg	**0.16** | **0.17**	**0.14** | **0.16**		0.04 | 0.07
	KE, 60º/s, Nm/Kg	**0.37** | **0.20**	**0.42** | **0.20**		**0.16** | 0.07
	KF, 60º/s, Nm/Kg	**0.40** | **0.33**	**0.42** | **0.32**		**0.17** | **0.13**
	KE, 0º/s, RFD, Nm/kg/s	**0.24** | **0.18**	**0.19** | 0.10		0.06 | 0.06
	KF, 0º/s, RFD, Nm/kg/s	**0.12** | 0.06	**0.11** | 0.04		0.02 | 0.01
	KE, 0º/s, RFD@200ms	**0.31** | **0.18**	**0.30** | 0.10		0.10 | 0.02
	Nm/kg/s	**0.26** | **0.17**	**0.29** | **0.12**		0.05 | 0.07
	KF, 0º/s, RFD@200ms Nm/kg/s				
Klaren et al. [62]	Strongest (S):	S:			
	KE, 0º/s, Nm	**0.34**			
Mañago et al. [15]	Weakest (W):	W:	W:		
	KE, 0º/s, kg/BMI	**0.28**	**0.34**		
	KF, 0º/s, kg/BMI	**0.47**	**0.44**		
	HE, 0º/s, kg/BMI	**0.25**	**0.27**		
	HF, 0º/s, kg/BMI	**0.33**	**0.42**		
	HAb, 0º/s, kg/BMI	**0.47**	**0.47**		
	HAd, 0º/s, kg/BMI	**0.30**	**0.37**		
	DF, 0º/s, kg/BMI	**0.32**	**0.29**		
Moller et al. [30]	Weakest (W) | Strongest (S):				W | S:
	KE, 0º/s (70º), Nm/kg				**0.59** | 0.09
	KF, 0º/s (30º), Nm/kg				**0.36** | 0.16
	HE, 0º/s (45º), Nm/kg				0.17 | 0.01
	HF, 0º/s (45º), Nm/kg				**0.36** | 0.24
	KE, 60º/s, Nm/kg/sec				**0.49** | 0.05
	KF, 60º/s, Nm/kg,sec				**0.40** | 0.09
Ng et al. [28]	Right (R):	R:			
	DF, 0º/s, RFD (% peak tetanic/ms)	**0.33**			
Pilutti et al. [68]	Strongest (S):	S:	S:		
	KE, 0º/s (60º), Nm (ID)	**0.33**	**0.47**		
	KF, 0º/s (60º), Nm (ID)	**0.36**	**0.47**		
Sandroff et al. [71]	Strongest (S):	S:	S:		
	KF, 0º/s, Nm	**0.53**	**0.43**		

Thoumie et al. [12]	Weakest (W) | Strongest (S):	W | S:	
	KE, 60º/s, Nm	**0.15** | **0.12**	
	KF, 60º/s, Nm	**0.22** | **0.19**	
Wagner et al. [29]	Weakest (W):	W:	W:
	PF, 0º/s, Nm/Kg	**0.29**	**0.29**
	DF, 0º/s, Nm/Kg	0.06	**0.17**
Yahia et al. [13]	Weakest (W) | Strongest (S):	W | S:	
	KE, 60º/s, Nm	**0.28** | 0.07	
	KF, 60º/s, Nm	**0.23** | **0.36**	

The R^2 values are presented for 1 or 2 limbs depending on how the results were reported in the original paper.

PF, plantar flexor; DF, dorsiflexor; KE, knee extensor; KF, knee flexor; HE, hip extensor; HF, hip flexor; HAb, hip abductor; Had, hip adductor; RFD, rate of force development. Bold font indicates statistical significance $p \leq 0.05$.

Associations between lower-extremity muscle mechanical function and lower-limb functional capacity across muscle groups and limbs

Figure 2 presents the association between muscle strength of different muscle groups of the weakest and strongest limb and specific measures of lower-limb functional capacity. The most frequently investigated muscle groups were the knee extensors and flexors, which were related to short and long walking performance (R^2 range = 0.18-0.34), TUG (R^2 range = 0.14-0.20) and sit to stand (R^2 range = 0.07-0.34) (significant according to mean R^2 and 95% CIs). The overall pattern showed comparable relationships between the knee flexors and extensors and functional capacity outcomes assessing short and long walking, and TUG and sit-to-stand (R^2 range = 0.11-0.34 vs 0.07-0.34) (significant according to mean R^2 and 95% CIs). In addition, we found a general pattern showing slightly stronger associations with the different lower-limb functional capacity outcomes for the weakest leg as compared with the strongest leg (R^2 range = 0.11-0.42 vs 0.00-0.34). Furthermore, the sit-to-stand test seemed to be the most sensitive outcome for identifying muscle strength asymmetry between the weakest and strongest limbs (R^2 range = 0.24-0.42 vs 0.07-0.34).

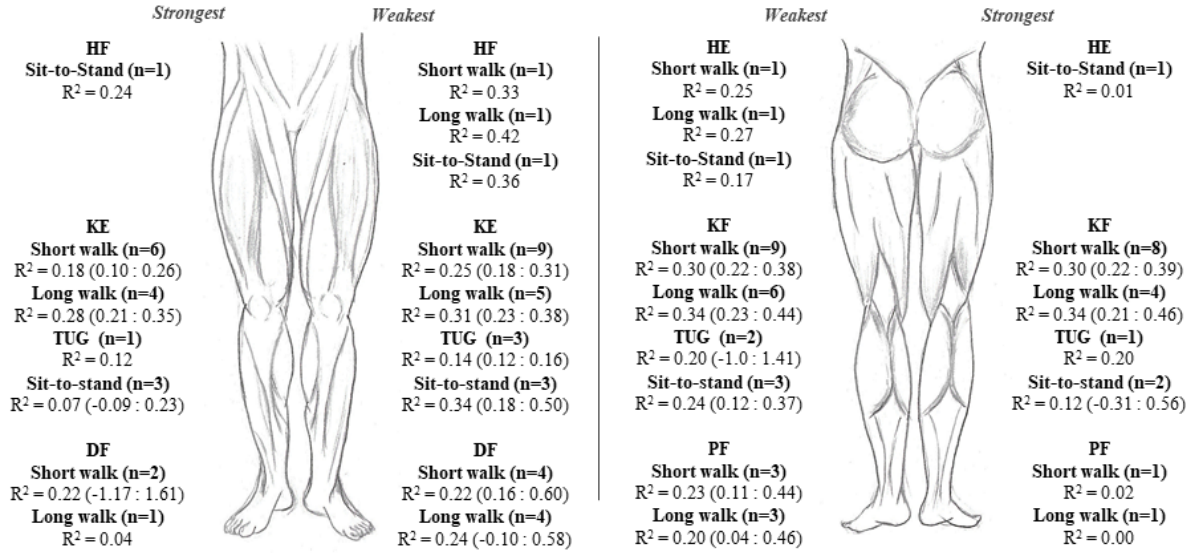

Figure 2. Association between lower-extremity strength of different muscles divided by the strongest and weakest leg and measures of lower-limb functional capacity. The R^2 values are presented as mean and 95% confidence intervals across studies adjusted for sample size and sex ratio. In the illustration, the right leg represents the strongest leg (although it could be different in individual study participants). HF: hip flexor; HE: hip extensor; KE: knee extensor; KF: knee flexor; DF: dorsi-flexor; PF: plantar-flexor.

Contraction types

Because data on isometric (0°/s) and dynamic (60°/s) muscle strength of both the knee extensors and flexors were frequently reported (Table 2), along with their association with walking capacity, these results were specifically selected and summarized in Table 3. Overall, muscle strength of both knee extensors and flexors showed comparable associations with short and long walking capacity outcomes when tested isometrically and dynamically (according to mean R^2 and 95% CIs; Table 3). The only exceptions were for the association between isokinetic knee extensor strength and long walk (2 studies only) and between knee flexor muscle strength and long walk (1 study only). Although based on limited data and thus not shown in Table 3, RFD for both the knee extensors and flexors appears to display similar associations with walking capacity as isometric and dynamic muscle strength (Table 2).

Table 3. Summary of associations between isometric (0°/s) and isokinetic (60°/s) muscle strength of the knee extensors and flexors and walking tests (short and long).

	KE				**KF**			
	Short		**Long**		**Short**		**Long**	
	Isometric	Isokinetic	Isometric	Isokinetic	Isometric	Isokinetic	Isometric	Isokinetic
	0.15 [32]	0.15 [32]	0.29 [32]	0.28 [32]	0.33 [32]	0.28 [23]	0.41 [32]	0.37 [10]
	0.31 [57]	0.38 [23]	0.18 [57]	0.31 [10]	0.21 [57]	0.21 [12]	0.18 [57]	
	0.35 [62]	0.14 [12]	0.38 [68]		0.29 [68]	0.30 [13]	0.41 [68]	
	0.27 [68]	0.18 [13]	0.48 [68]		0.36 [68]	0.37 [10]	0.48 [68]	
	0.34 [68]	0.29 [10]	0.22 [10]		0.17 [10]		0.15 [10]	
	0.20 [10]	0.09 [60]	0.18 [14]		0.53 [71]		0.44 [71]	
	0.22 [14]		0.35 [15]		0.19 [14]		0.14 [14]	
	0.28 [15]				0.48 [15]		0.45 [15]	
mean	**0.26**	**0.17**	**0.29**	**0.30**	**0.30**	**0.33**	**0.32**	**0.37**
(CI)	(0.19 : 0.32)	(0.09 : 0.26)	(0.18 : 0.40)		(0.19 : 0.41)	(0.14 : 0.51)	(0.17 : 0.47)	

Data are presented as R^2 [article reference]. The mean R^2 values and their 95% confidence intervals (CIs) are adjusted for sample size and sex ratio. KE, knee extensor; KF, knee flexor;

Discussion

The primary purpose of this systematic literature review was to identify studies that measured lower-extremity muscle mechanical function and lower-limb functional capacity (e.g., walking, dynamic balance and chair rise) in PwMS. Findings across studies showed that lower-extremity muscle mechanical function (predominantly muscle strength) explained a significant part of the variance in lower-limb functional capacity tests (approximately 20–30%). This was particularly evident in muscle mechanical function outcomes from the weakest leg. In addition, the most frequently reported associations were knee extensor and flexor muscle strength, which overall explained the same part of the variance in walking capacity. Overall, lower-extremity muscle mechanical function most frequently was evaluated by using isokinetic dynamometry while performing maximal isometric (0°/sec) and dynamic contractions at slow contraction velocities (30-60°/sec). Short walking tests such as the T25FWT and the 10-min walk test were the most frequently performed functional capacity tests. Despite the large number of studies (n = 59) evaluating lower-extremity muscle mechanical function and lower-limb functional capacity outcomes, only a subset of these (n = 17) reported the association between muscle mechanical function (predominantly muscle strength) and functional capacity, which limited the number of findings that could be mapped.

Lower-extremity muscle groups and lower-limb functional capacity

The reviewed articles predominantly evaluated muscle strength of the knee extensors and flexors, generally revealing large heterogeneity between study findings. This systematic review clearly shows that testing of hip muscle strength (and to some extent plantar flexor

muscle strength), and relating this to lower-limb functional capacity has not gained much attention in MS research. Møller et al. [30] reported a significant association between hip flexor muscle strength (but not hip extensor muscle strength) of the weakest leg and the sit-to-stand test. In addition, Mañago et al. [15] reported significant associations between lower-extremity muscle strength from hip muscles and walking capacity. In addition to evaluation of hip flexors and extensors, Mañago et al. [15] emphasized the importance of the hip abductor and adductor muscle strength on walking performance. To compensate for weakness of major muscle groups during walking, such as the hip extensors and knee flexors, an increase in the contribution from the ankle plantar flexors has been shown, thereby revealing the plantar flexors as an important muscle group during support, forward propulsion and swing initiation in normal walking [31]. This notion can nevertheless not be inferred from the present data because it would require a longitudinal study with multiple test sessions to examine the time course of strength changes in different (e.g., distal versus proximal) muscle groups.

Broekmans et al. [32] found stronger associations with walking capacity for knee flexor than knee extensor muscle strength in MS patients (R^2 range 0.10-0.53 vs 0.07-0.30). Previous studies [33,34] in older individuals have suggested that a non-linear S-shaped relationship exists between lower-extremity muscle strength and walking capacity (i.e., with the association wearing off when muscle strength is very low and very high, respectively). Hence, the observations by Callesen et al. [14], may reflect that the level of knee extensor (and plantar flexor) muscle strength in PwMS walking less than 400 m during the 6MWT do not affect walking capacity, whereas walking more than 400 m during the 6MWT the level of knee extensor (and plantar flexor) muscle strength do impact walking capacity. This notion did not agree with Thoumie et al. [12], where associations between knee extensor muscle strength and functional capacity did not differ between less and more disable PwMS. However, the authors reported a stronger association between knee flexor muscle strength and

lower-limb functional capacity in less disabled PwMS. Taken together, the findings of the present systematic review suggest that muscle strength of both hip, knee and ankle muscle groups are related to lower-limb functional capacity in ambulatory PwMS (explaining approximately 20-30%). It is likely that the strength of the association may depend on whether the muscle group acts as an agonist or antagonist to a particular movement and whether patients are mild, moderately or severely impaired. Nevertheless, the latter was not supported by data from the present study in that EDSS score did not affect the associations between lower-extremity muscle strength and walking capacity (data not shown). This may have been due to the narrow range of EDSS scores (i.e. from 2.8 to 6.5) along with the heterogeneity in lower-limb functional capacity tests across the included studies.

Strongest versus weakest limb

An interesting finding of the present study was the stronger relationships between lower-extremity muscle mechanical function and lower-limb functional capacity outcomes observed in the weakest versus the strongest leg. Intuitively this makes sense, because the weaker leg would likely be more limiting to lower-limb functional capacity than the stronger leg. Defining the weakest leg can nevertheless be difficult because some muscle groups may be stronger in one leg, whereas other muscle groups are stronger in the other leg. Moreover, an affected leg following a relapse may still be stronger than the non-affected leg. Keeping that in mind, the most direct approach is by establishing the degree of muscle strength asymmetry between legs (i.e., by testing both legs and calculating the percentage difference). Studies suggest clinically important strength asymmetries if the difference exceeds 10% [33], which is a clinical cut-off point that could be applied to more appropriately investigate the effects of the lower-extremity muscle strength asymmetry in functional capacity of PwMS. Leg asymmetry has been shown to be associated with walking capacity in PwMS (i.e., with slower

walking speed and T25FWT [6,35]), but Proessl et al. [36] did not find associations between knee extensor strength asymmetry and walking ability and fatigability in PwMS. Also, a study from Kalron et al.[37] revealed no incidence of asymmetry of the vertical ground reaction force during gait in PwMS along with no association with walking and balance. As suggested in MS studies, the weaker leg and the resulting asymmetry in lower-extremity muscle strength likely lead to decreased performance during lower-limb functional capacity tests. This situation may be due to the need for equivalent force production by the knee extensor and flexor muscles to perform symmetrical movements to lower the energy cost [33]. In this way, in PwMS, the stronger leg may lower its strength production to equate with the weaker leg, thereby leading to an overall decrease in functional capacity performance over time. Another theory may relate to the stronger leg trying to compensate for the weaker leg, which over time could further increase the gap between the legs. However, it does seem that the weakest "link of the chain" is the main determinant of lower-limb functional capacity, making it less likely that the strongest leg can fully compensate for the weaker leg. Also of note, the results from this review suggest that the sit-to-stand test was the most sensitive functional capacity measurement of knee muscle strength disparity. The walking tests also revealed a strength difference between the plantar flexors, but only one article reported the R^2 value for the strongest leg.

Dynamic versus isometric contractions

As shown in this review, lower body muscle strength in most cases explains 20% to 30% of the performance in lower-limb functional capacity tests. Of note, the present review did not find any major difference between the relationship of isometric (0°/sec) or dynamic (60°/sec) muscle strength and lower-limb functional capacity tests in PwMS, the former being most frequently reported. An obvious explanation is that dynamic muscle contractions were

performed at a rather slow velocity (i.e., 60°/sec), whereas most physical tasks performed maximally may require moderate-to-fast velocity muscle contractions (i.e., > 60°/sec). Moreover, impairments in lower-extremity muscle strength (also including "explosive" strength) and power have been shown to be much more pronounced during fast concentric muscle contractions as compared with both slow concentric, isometric and eccentric contractions [8]. We did not identify any studies examining the relationship between lower-extremity muscle power and lower-limb functional capacity, but knee extensor and knee flexor RFD (based on 3 studies only) appeared to display similar relationships to walking capacity as isometric and dynamic muscle strength. The latter has also been observed in a large-scale cohort study of older individuals [34]. Studies examining relationships between lower-extremity muscle RFD or power and lower-limb functional capacity in PwMS are thus clearly warranted.

Clinical implications

On the basis of the included cross-sectional studies, the relationships between lower-extremity muscle mechanical function and lower-limb functional capacity in PwMS suggest that a PwMS can improve lower-limb functional capacity by improving lower-extremity muscle strength or vice versa (i.e., when undergoing disuse or detraining). Indeed, studies have shown that rehab- or exercise-induced improvements in lower-extremity muscle strength translates into improvements in functional capacity tests assessing walking [38], TUG [39,40], sit-to-stand and stair climbing [41–43]. This suggests a causal relationship, in which lower-extremity muscle mechanical function is a modifiable factor that directly influences lower-limb functional capacity in PwMS. Among the many different types of rehab/exercise interventions, the most robust results were from studies evaluating high-intensity progressive resistance training (PRT) [42]. Indeed, 6 to 24 weeks of high-intensity PRT has been shown

to elicit muscle strength improvements in ankle dorsiflexors [40], knee extensors [41,42,44] and flexors [41,44] that were translated into functional capacity improvements and particularly walking performance [40–42,44]. An interesting observation from the study by Kjølhede et al. was that some of the strength exercises were performed unilateral, ultimately generating more neuromuscular and strength adaptations in the weakest leg [42]. This relates well to findings of the present review showing that the weakest leg is stronger associated to functional performance.

Our overall interpretation of the present findings, which most frequently investigated the association between knee extensor or flexor muscle strength and walking capacity, is that no lower-extremity muscle group is the main driver of lower-limb functional capacity. Hence, we would recommend that rehab/exercise interventions target all lower-extremity muscle groups acting over the ankle, knee, and hip joint. If known, the weakest leg could be specifically targeted by additional unilateral exercises. Moreover, it seems prudent to address aspects other than high-intensity PRT, for instance by involving elements that target motor control and balance. Indeed, recent studies have provided evidence that force steadiness (i.e., force fluctuations during submaximal contractions ≈ motor control) of the ankle plantar flexor and dorsiflexor muscles [27,45] along with lower-limb balance [14] also influences walking performance in PwMS. Altogether, we would recommend that high-intensity PRT serve as the core of rehab/exercise interventions supported by the other aspects, to improve lower-limb functional capacity in PwMS.

Methodological considerations

A number of methodological considerations has to be kept in mind when interpreting the results of the present review. First, all the studies reporting associations used a cross-sectional study design, which is neither causality nor the direction of the relationship can be established

with certainty. Second, heterogeneous studies in terms of MS populations (comprising relapse-remitting, primary progressive and secondary progressive MS types along with differences in MS disease severity), strength testing with different equipment (hand-held and isokinetic dynamometry), different strength outcomes (e.g., peak torque, power and RFD), and different functional capacity tests, limit direct comparison across the included studies.

Conclusion

In PwMS, lower-extremity muscle strength of the weakest limb explains 20% to 30% of the performance in functional capacity tests comprising walking and sit to stand, independent of lower-extremity muscle group, contraction type and velocity. Exercise programs for PwMS should focus on increasing muscle mechanical function and on exercises that could minimise strength asymmetry between limbs.

Funding. This work was partially funded by the Coordination for the Improvement of Higher Education (CAPES, Brazil – Finance Code 001).

Conflict of interest. CR and ACD declare no conflict of interest. LGH has received research support, travel grants and/or teaching honoraria from Biogen and Sanofi Genzyme. UD has received research support, travel grants and/or teaching honorary from Biogen Idec, Merck Serono, Novartis, Bayer Schering and Sanofi Aventis as well as honoraria from serving on scientific advisory boards of Biogen Idec and Genzyme.

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3.2 Artigo 2 – Publicado

KNEE FLEXOR STRENGTH AND BALANCE CONTROL IMPAIRMENT MAY EXPLAIN DECLINES DURING PROLONGED WALKING IN WOMEN WITH MILD MULTIPLE SCLEROSIS

Cintia Ramari [a], Andréa G. Moraes [a], Carlos B. Tauil [b,c], Felipe von Glehn [d]; Robert Motl [e], Ana C. de David [a]

[a] Faculty of Physical Education, University of Brasília, DF, Brazil

[b] Base Hospital, Department of Neurology, Brasília, DF, Brazil

[c] Faculty of Medicine, University of Brasília, DF, Brazil

[d] Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[e] Department of Physical Therapy, University of Alabama at Birmingham, AL, US

Revista: MULTIPLE SCLEROSIS AND RELATED DISORDERS

Fator de impacto: 2.88

https://doi.org/10.1016/j.msard.2018.01.024

ARTICLE HISTORY:

Received 9 November 2017

Accepted 25 January 2018

Abstract

Background: Physiological factors such as muscle weakness and balance could explain declines in walking distance by multiple sclerosis (MS) patients. The purpose of this study was to characterize levels and examine associations among decline in walking distance, balance and muscular strength in women with mild MS. Methods: Participants included 28 women with mild relapsing-remitting MS and 21 women without MS. We executed the 6-minute walk test (6MWT) to verify declines in walking distance. Isokinetic knee flexion (KF) and extension (KE) muscle strength was measured using a dynamometer. Balance was quantified using a force platform, with eyes open and closed, on a rigid and foam surface. Results: The MS patients presented declines in walking, lower KF muscle strength, and worse balance than controls. KF strength and balance correlated with walking in the MS group. The KF strength explained differences between groups in walking. The KF strength and balance presented as predictors of walking slowing down in the 6MWT, in mild MS. Conclusion: Women with mild MS have strength impairment of knee flexor muscles and balance control impairment that may explain walking related motor fatigability during prolonged walking.

Keywords: Six-minute walking; distance-walked-index; strength; balance; multiple sclerosis; relapsing-remitting.

1. Introduction

Multiple sclerosis (MS) is a chronic disabling disease that is seemingly trigged by environmental factors in genetically susceptible people. MS most frequently occurs among young and middle-aged women of European descendent and presents with a relapsing-remitting (RRMS) course in approximately 85% of cases (1). One recent systematic review (2) reported that predictors of long-term disability in the Brazilian population further were similar with Caucasian populations. Concerning symptomatic manifestations, motor disorders were most frequent (36%) in Brazilians with MS followed by sensory (27%).

Regarding motor disorders, walking performance over longer distances, such as the 6-minute walk test (6MWT), provide assessment of walking fatigability, maximal walking distance, and functional capacity (3) and predict declines in everyday activities such as habitual walking (4). The 6MWT is one of the best characterized measures of walking endurance in persons with MS (5–7). Persons with MS have reduced 6MWT performance compared with

matched controls (8,9), and this reduction may be associated with lower extremity strength and postural control (i.e., balance) (10–13). In addition, recent studies suggest the importance in identify factors, such as muscle weakness and others MS related symptoms – spasticity, cerebellar signs, and sensory integration in balance, in order to explain declines in walking distance and possible altered pacing strategy adopted by MS patients (14).

This study (1) characterized walking capacity, balance and muscular strength in women with mild RRMS, (2) examined the percentage change in distance walked in the 6MWT, and its associations between muscular strength, and postural control, and (3) investigated possible physiological deconditioning predictors of walking impairment in persons with mild MS, based on lower limb strength and balance impairment. Such research is important for identify factors from strength and balance which could predict walking variabilities in persons with mild disability MS. From that, is important for establishing the basis of rehabilitation interventions that focus on exercise training as an approach for improving mobility in patients with MS.

2. Methods

Participants included 28 women with MS and 21 women without MS who were matched on age, height, weight, and self-reported habit of physical activity by answering questions about engagement in systematized programs of physical exercise. We obtained the written informed consent prior to procedures and the Ethics Committee from the Department of Health/Federal District - Brazil approved this project, with the protocol number: 67098217.5.0000.5553. Inclusion criteria were (1) aged 18 years or older; (2) diagnosis of relapsing-remitting (RR) MS course; (3) ambulatory and capable to complete the 6MWT; (4) relapse free over the past 30 days; and (5) mild MS disability as evidenced by a rating on the Expanded Disability Status Scale (EDSS) between 1-3. Exclusion criteria were (1) unable to understand the motor tests commands; (2) non-controlled chronical medical conditions, such as hypertension, diabetes and cardiac conditions; and (3) neurologic conditions in addition to MS.

2.1 Walking functional capacity

In the 6MWT participants were instructed to walk as fast and as far as possible without rest or encouragement for 6 minutes. The 6MWT was completed within a single corridor measuring ten-meter in length, with cones placed on opposite ends, while performing 180° turns around the cones (15). We placed two photocells (Cefise - Speed Test Fit, Brazil) on the corridor in order to note the distance traveled minute-by-minute.

2.2 Muscular strength

We measured the dynamic isokinetic muscle strength by an isokinetic dynamometer (Biodex Medical Systems 3, Inc., USA). The range of motion was kept within 0–80° for the knee joint. Bilateral isokinetic (concentric/concentric) flexion and extension of the knee at 60°/s, 90°/s and 180°/s was performed four times. Patients had two minutes of rest between the series and verbal encouragement was standardized.

2.3 Balance

Balance was based upon the displacement of the center of pressure (COP) quantified using a force platform (AccuSway Plus, AMTI Inc, USA). Subjects were asked to stand upright barefoot on the force platform with heels separated by 3 cm. During testing with the eyes open subjects looked at point located at the distance of 1.5 m. The data were acquired during 30-second with open and closed eyes on a rigid and on an unstable surface with a plastic foam. Participants executed three trials of each condition with 60 seconds of rest interval. COP velocity (COP-vel) and area of 95% ellipse (COP-area) were recorded with a sample frequency of 100 Hz, and a Butterworth digital filter with cutoff frequency of 10 Hz was used.

2.4 Data analysis

All data analyses were performed in the SPSS program (SPSS 13.0, SPSS Inc., USA). The Shapiro-Wilk test examined the normality of the data. Regarding between-group comparison, the student's t-test for independent samples were conducted and, the Mann-Whitney test were executed on COP-area outcomes. Analysis of variance (ANOVA) with repeated measures was conducted for examining group differences on peak torque and COP-vel. Where necessary, Tukey's post-test was conducted. For the COP-area, the Friedman test was used followed by the Wilcoxon test. To measure the decline in distance walked, we calculated the percentage change in distance walked – distance walked index (DWI), starting from the second minute (14). The DWI was calculated using the following equation:

$$DWI = \frac{Distance\ walked\ at\ minute\ n - Distance\ walked\ at\ minute\ 1}{Distance\ walked\ at\ minute\ 1}\ x\ 100$$

We calculated the DWI in each minute of the test (DWI2-1, DWI3-1, DWI4-1, DWI5-1 and DWI6-1). ANOVA was performed in order to investigate differences between groups, and differences between the DWIn-1 over the course of the 6MWT. Where necessary, Tukey's post-test was conducted. Depending on data distribution, we conducted the Pearson or

Spearman correlations between the DWI6-1 and muscle strength and balance. We executed two types of multivariate linear regression analysis: hierarchical and stepwise. The hierarchical linear regression examine which variables accounted for group differences in the DWI6-1. Group entered in the first step, and the variables from strength and balance were added in the step 2 and 3, respectively. To examine if a combination of predictors would explain more variance in the DWI6-1 for persons with MS, the variables which were significantly different between groups and had correlation with DWI6-1 were entered in a multivariate stepwise analysis. The level of significance adopted was 0.05.

3. Results

Demographic and clinical values are presented in Table 1. There were no significant difference in age, height and weight, $p>0.05$, between groups. All patients with MS had a RRMS disease course with a short disease duration and mild level of disability based on EDSS scores.

Table 1. Demographic characteristics of individuals with MS and controls without MS.

Variable	MS (n = 28)	Controls (n = 21)
Age, y	33.9 (9.2)	32.1 (7.7)
Height, cm	160.8 (5.1)	161.8 (4.7)
Weight, kg	62.2 (12.1)	60.4 (9.1)
EDSS, median (range)	2.5 (1-3)	
MS onset, y	4.9 (3.9)	
MS course	RR	

Caption of Table 1: EDSS, Expanded Disability Status Scale; RR: Relapsing-Remitting

As shown in Figure 1, there is a significant slowing down over the course of the 6MWT by MS patients. Controls did not present any significant difference over time regarding the DWI. The analysis between groups revealed a significant statistical difference at minute 6 (adjusted p-value = 0.019), with higher negative percentage change in the DWI6-1 presented by the MS population. Persons with MS walked significantly less compared to controls in the 6MWT, see Table 2.

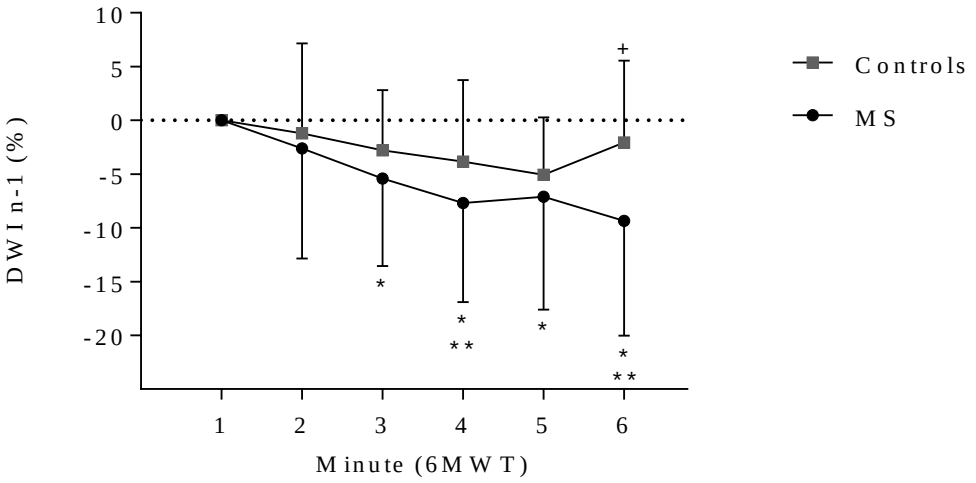

Figure 1. The percentage Distance Walked Index (DWIn-1) over time of the 6MWT. * Denotes statistical significance at $p<0.05$ compared to the distance walked during minute 1 (percentage change = 0). ** Significantly different from DWI2-1. + Statistical difference ($p<0.05$) between control and MS group.

Regarding knee muscle strength, the results (Table 2) reveled differences between groups in the knee flexion (KF) peak torque. At 60 º/s velocity, persons with MS achieved lower values of KF strength for both legs. At 90 º/s velocity, the MS patients showed lower strength in the KF muscle of the left leg. Whereas the KF of the right leg achieved a lower value of peak torque at 180 º/s velocity.

As indicated in Table 2, persons with mild MS had higher values of COP-vel and area compared to controls. However, the differences occurred in the rigid surface with eyes closed and in the foam surface with eyes open, with $p<0.05$.

Table 2. Group differences in walking, knee muscle strength and balance.

Variable	MS	Controls	*p* value	*d* (CI)
6MWT				
Distance	506.2 (61.1)	588 (46.6)	<0.0005*	-1.50 (-17.6 14.5)
Strength				
PT 60 º/s (N-m)				
KE / RL	113.3 (26.7)	125.4 (23.8)	0.122	-0.48 (-7.75 6.78)
KE / LL	109.9 (25.7)	120.4 (25.7)	0.182	-0.41 (-7.75 6.92)
KF / RL	51.2 (17.4)	64.9 (13.9)	0.008*	-0.87 (-5.43 3.67)
KF / LL	54.2 (15.3)	67.0 (19.8)	0.019*	-0.75 (-5.73 4.22)
PT 90 º/s (N-m)				
KE / RL	107.4 (27.4)	116.2 (20.1)	0.238	-0.36 (-7.35 6.61)

KE / LL	102.7 (23.8)	111.5 (21.1)	0.206	-0.39 (-6.86 6.07)
KF / RL	54.5 (17.4)	62.8 (13.8)	0.090	-0.53 (-5.07 4.01)
KF / LL	53.0 (14.2)	61.8 (10.0)	0.025*	-0.71 (-4.29 2.85)
PT 180 º/s (N-m)				
KE / RL	80.6 (20.0)	89.7 (15.5)	0.104	-0.51 (-5.69 4.67)
KE / LL	76.7 (19.2)	86.0 (14.1)	0.079	-0.55 (-5.44 4.33)
KF / RL	43.7 (14.2)	52.1 (11.2)	0.037*	-0.66 (-4.36 3.03)
KF / LL	44.5 (13.4)	51.0 (8.6)	0.067	-0.57 (-3.86 2.71)
Balance				
Rigid Surface				
COP-vel / EO (cm/s)	1.0 (0.2)	0.9 (0.1)	0.222	0.62 (0.57 0.66)
COP-vel / EC (cm/s)	1.5 (0.5)	1.1 (0.1)	0.019*	1.07 (0.96 1.17)
COP-area / EO (cm^2)	3.3 (3.1)	2.0 (0.8)	0.776	0.55 (-0.09 1.20)
COP-area / EC (cm^2)	5.4 (4.5)	3.2 (1.5)	0.191	0.63 (-0.31 1.59)
Foam Surface				
COP-vel / EO (cm/s)	2.3 (0.9)	1.6 (0.2)	0.002*	1.03 (0.85 1.22)
COP-vel / EC (cm/s)	5.6 (1.9)	4.3 (1.0)	0.065	0.84 (0.41 1.27)
COP-area / EO (cm^2)	7.9 (6.1)	4.0 (1.2)	0.060	0.85 (-0.40 2.11)
COP-area / EC (cm^2)	32 (18.9)	19.4 (8.1)	0.191	0.84 (-3.26 4.96)

Caption of table 2: PT, Peak Torque; KE, Knee Extension; KF, Knee Flexion; RL, Right Leg; LL, Left Leg; COP-vel, Center of Pressure-velocity; EO, Eyes Open; EC, Eyes Closed. *d*, Cohen's d. CI, 95% confidence interval. Note: Data are presented as mean (SD). * Denotes statistical significance at $p < 0.05$.

The bivariate correlations revealed associations between KF peak torque 60 º/s and DWI6-1 (Pearson correlation coefficient, R = 0.50, $p<0.05$), and between KF peak at 180 º/s and DWI6-1 (Pearson correlation coefficient, R = 0.48, $p<0.05$), only for the MS group. The DWI6-1 was correlated to COP-area in the foam surface with eyes closed for persons with MS (Spearman correlation coefficient, R = -0.42, $p<0.05$), and to COP-area in the rigid surface with eyes open (Pearson correlation coefficient, R = 0.53, $p<0.05$) for the controls.

The hierarchical regression analysis showed in the first step that the group explained 13% of the variance in the DWI6-1. In the second step we included the KF strength at 60 º/s (R2 = 0.272), which significantly explained 14% of variance in walking. We also included the balance variables in a third step. However, this model was not significant. Suggesting that COP-vel did not contribute for walking variance explanation (see Table 3).

In the stepwise regression analysis for the MS patients, besides the variables, which were different between groups, we included the COP-area with eyes closed in the foam surface, because it was correlated with DWI6-1. The stepwise retained the KF peak torque of the right

leg at 60 º/s, and the COP-area with eyes closed in the foam surface. With a R2 = 0.395, the variables explained 39% of variance in walking performance (see Table 3).

Table 3. Summary of multiple linear regression analysis with hierarchical regression and with stepwise for predicting variance in walking.

Regression and Variables	B	SE B	β
Regression Type: *Hierarchical*			
Step 1			
Group	6.750	2.830	0.361*
Step 2			
Group	4.685	2.821	0.250
KF/RL - PT 60 º/s	0.265	0.122	0.480*
KF/LL - PT 60 º/s	-0.062	0.108	-0.126
Step 3			
Group	3.437	3.118	0.184
KF/RL - PT 60 º/s	0.209	0.137	0.379
KF/LL - PT 60 º/s	-0.017	0.118	-0.034
RS: COP-vel/EC	0.073	3.689	0.004
FS: COP-vel/EO	-2.094	2.362	-0.181
Note: R^2 = 0.130 for step 1 (p<0.05); R^2 = 0.272 for step 2 (p<0.05); R^2 = 0.295 for step 3 (p>0.05).			
* Denotes statistical significance at p<0.05.			
Regression Type: *Stepwise*			
KF/RL - PT 60 º/s	0.234	0.097	0.418*
FS: COP-area/EC	-0.194	0.087	-0.389*
Note: R^2 = 0.395 for model. * Denotes statistical significance at p<0.05.			

Note: KF/RL - PT 60 º/s = Knee Flexion/Right Leg - Peak Torque at 60 º/s; KF/LL - PT 60 º/s = Knee Flexion/Left Leg - Peak Torque at 60 º/s. *RS*: COP-vel/EC = *Rigid Surface*: Center of Pressure velocity/Eyes Closed; *FS*: COP-vel/EO = *Foam Surface*: Center of Pressure velocity/Eyes Open; *FS*: COP-area/EC = *Foam Surface*: Center of Pressure area/Eyes Closed.

4. Discussion

The findings of this cross-sectional study were: (a) women with mild MS presented a continuous slowing down over the 6MWT, lower KF muscle strength, and worse balance than controls without MS; (b) correlations between KF strength, balance and DWI6-1 in MS patients; (c) KF strength, but not balance, explained differences in DWI6-1 between MS patients and controls; (d) KF strength at 60 º/s, and COP-area in the foam surface with eyes closed, were predictive variables which explained the variance in DWI6-1 among MS patients.

As shown by previous research (9) we demonstrated that mild MS patients walked less in the 6MWT compared to controls. There is differences between groups in DWIn-1, specifically in the DWI6-1. Persons with MS decelerated walking after the third minute, when compared to the first minute walked. In addition, the deceleration in the fourth and sixth minute was higher with differences from the second minute. Our findings corroborate with others studies (16,17), and suggest a pacing strategy by MS patients, reporting a faster walking speed during the first 2 minutes of the 6MWT. Leone C. et al. (14), also reported a significant decrease in DWIn-1 over time from the second to the sixth minute, throughout the 6MWT, in patients with MS. The control group did not change their pacing strategy during the 6MWT, and tended to accelerate in the last minute, however the difference between DWI5-1 and DWI6-1 was not significant. In part, our study corroborate the findings from Rémy Phan-Ba et. al. (18), who suggested a mild acceleration at the end of a 500 meters walking test by the healthy controls compare to mild MS patients.

There were differences in KF strength between groups. Studies suggest that muscle strength in MS is impaired (11,12,19,20). Our results did not identify differences between MS and controls regarding KE strength, and this is in contrast with the study of Yahia (12). A possible explanation is the differences of participant characteristics such as disease duration and biological sex. However, our finding of impairment in KF strength is consistent with the literature (9,11,12,20–22).

The differences in balance between groups were readily apparent in the rigid surface with eyes closed and in the foam surface with eyes open. All differences is concerning to COP-vel. Our results suggest that there is balance impairment associated with MS affected by the integration of sensory component. Porosiñska et al. (23) demonstrated differences in balance between MS patients and controls in all conditions: rigid with eyes open and closed; foam with eyes open and closed. Morrison et al.(24) also found differences between MS and controls, and they emphasized the greatest disparity during the more challenging balance tasks (i.e. when vision was withdrawn and a foam surface was used).

We found associations between peak torque values, balance and DWI6-1. There was significant correlation between KF strength and DWI6-1 from the 6MWT only for the MS group. Yahia et. al.(12) reported significant correlation between gait parameters measured and the peak torque for the KE and KF. Kjølhede et al (11) reported that maximal strength was a predictor of walking performance in persons with MS. Regarding balance, the COP-area

performed with eyes closed in the foam was correlated to walking capacity in the MS group. Sandroff et. al.(9) also reported bivariate correlation between COP area and 6MWT distance. However, the test was performed in a rigid surface with eyes opened.

The hierarchical regression analysis identified the KF strength as a strong predictor of group differences. Balance parameters such as COP-vel, which revealed to be different between MS and controls, did not contribute for variance between groups. Our findings corroborate the results from Sandroff et. al. (9), where that balance did not explain group differences in gait variables. The stepwise multiple linear regression analysis retained the KF peak torque at 60 º/s and the COP-area from a foam surface with eyes closed in the equation. Thus, the combination of a weak KF muscle and the difficulty in control the posture in the most challenge task (foam surface with eyes closed), explained 39% of variance of the DWI6-1 in persons with mild disability MS. A kinematic gait analysis of patients with mild and moderate MS (10) revealed that minimum KF strength correlated highly with the peak KE moment in mild MS. Beyond that, MS patients with moderate degree had poor KF during the swing phase of the gait and the muscle strength correlated with the knee range movement. Those facts contribute to gait impairments, such as shorter swing phase, decrease of stride length and slower gait speed.

The altered sensory integration for balance control as shown by the COP-vel variable, the relation between COP-area with 6MWT and, the impairment in KF strength, suggested a possible motor compensation on walking by mild MS patients. Decrease in walking capacity, influenced by physical and sensory integration impairment, could partially influence a sedentary lifestyle that elicits multiple negative physiological changes (19), once persons with MS seem to be less physically active than controls (25). The literature shows that sedentary time is associated with disability, walking functional capacity and walking speed, particularly in patients with worse disability status of MS (26). From those observations, future research should focus on physical activity and efficient methods of adherence in physical practice for people with MS. Our results also highlight the importance of strength training to improve muscles functions, specifically the strengthening of KF muscle early in programs delineated to MS patients, since the disease diagnosis. We also emphasize possible significance of balance training, which contributes to a better sensory integration among the proprioception, visual and vestibular systems.

We conducted this study evaluating the percentage change in distance walked in the 6MWT and its physiological correlates e possible predictors based on muscle strength and postural

control in women with mild MS, but there are some limitations. These include no performed kinematic analysis to verify the influence of knee strength during the gait; the sample comprised only women with mild RRMS; different types of medications taking by the patients.

5. Conclusions

Findings of the present study indicated that women with mild MS presented decline in walking distance over the 6MWT, low knee flexor muscle strength and impaired integration in the sensory systems involved in balance, compared to women without MS.

Finally, the knee flexor strength explained differences between groups in walking. In addition, the knee flexor strength and balance, in the most challenged task (foam with eyes closed), presented as predictors of walking slowing down in the 6MWT, and may explain walking related motor fatigability during prolonged walking in patients with mild MS.

These results highlight the importance of interventions for reducing the decline in prolonged walking performance in women with mild MS, and our data suggest that this might be accomplished through exercise training programs that target lower extremity muscle strength, particularly the knee flexors, and balance exercises with altered sensory conditions.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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3.3 Artigo 3

Article category: Original Article

Title: MOBILITY, WALKING CAPACITY AND COGNITIVE FUNCTION ARE IMPAIRED IN PEOPLE PRESENTING WALKING-RELATED MOTOR FATIGUE IN MULTIPLE SCLEROSIS

Cintia Ramari 1; Ana Regina Diniz 1,2; Carlos B. Tauil 3; Flávia Martins da Silva 4; Felipe von Glehn 5; Robert W. Motl 6; Ana C. de David 1.

1. Faculty of Physical Education, University of Brasília, Brasília, Brazil
2. Faculty of Ceilândia, University of Brasília, Brasília, Brazil
3. Faculty of Medicine, University of Brasília, Brazil
4. Department of Psychology, Base Hospital Institute, Brasília, Brazil
5. Institute of Biology, University of Campinas, Campinas, Brazil
6. Department of Physical Therapy, University of Alabama at Birmingham, Birmingham, United States

Abstract

Objectives: this study identified differences in mobility, walking capacity and cognitive function between people with multiple sclerosis differing in walking-related motor fatigue. **Patients and Methods:** participated in this study 58 persons with multiple sclerosis. To assess mobility and walking capacity the timed up and go test, the timed 25-foot walk, and the six-minute walking test were performed. The symbol digit modality test measured cognitive function. The distance walked index was calculated between minute 6 and 1 of the six-minute walking. Participants were allocated into the fatigable group (distance walked index ≤−15%) and in the non-fatigable group. **Results:** the prevalence of walking-related motor fatigue was 39.6% in our sample. Comparing the fatigable versus the non-fatigable groups, the fatigable people with MS walked shorter distance in the six-minute walking test (243.7 m vs 405.2 m), expended more time to complete the timed up and go test (13.7 s vs 8.4 s), the timed 25-foot walk speed was lower (1.03 m/s vs 1.51 m/s) and scored less in the symbol digit modality test (34.8 vs 43.8). **Conclusion:** even controlling for demographics and disease characteristics, fatigable people with multiple sclerosis presented mobility, walking capacity and cognitive function impairments.

Key words: multiple sclerosis; walking speed; walk test; fatigue; mobility limitation; cognition.

1. Introduction

Multiple sclerosis (MS) is the most common autoimmune inflammatory disorder of the central nervous system and a leading cause of disability in young adults worldwide [1]. The pathological hallmark of MS is the accumulation of demyelinating lesions that occur in the white matter and the grey matter of the brain and spinal cord progressing with neuronal loss over time [2–4]. Clinically, MS patients demonstrate a variety of neurological signs and symptoms associated with neuroinflammation and degeneration of the central nervous system, with great impact on physical, social and mental functioning [5,6].

In symptoms related to mobility and spasticity domains, worsening impairment had been observed over three decades of the disease [5]. In addition, walking impairment and, or inability to ambulate, affects more than 68% of MS patients [7]. Compared to healthy controls, people with MS walk with slower velocity during the timed 25-foot walking (T25FW), and shorter distance during the six-minute walking test (6MWT) [8–10]. Lower walking speed had been associated with muscle strength and postural control impairment [11–14], high cognitive-motor interference [15–17], and subjective fatigue in the physical subdomain [18]. Regarding to impairment in cognitive processing speed, it had been also correlated with lower walking speed [19] and fatigue in people with MS [20].

Fatigue, a symptom that affected between 70 to 90% of people with MS, have been highly associated with poor quality of life [21]. Quantification of motor fatigue in MS has been referred as *fatigability* - defined as the magnitude of change in performance relative to an objective criterion over a period of time, or before and after a given fatiguing task [22]. In order to investigate motor fatigue in MS, Leone et al [23] evaluated the prevalence of walking-related motor fatigue according to MS phenotype and disability level in 208 people with MS. This multicentre study calculated the percentage of change in distance walked (distance walked index, DWI) in the 6MWT. A threshold of DWI $\leq$ -15% was chosen to classify the walking-related motor fatigue, which was identified in almost half of the more disabled patients, including those having progressive MS course. The slowing down in walking distance was also observed in our previous study, and it had been associated to muscle strength and balance impairment [24]. Although more studies are needed, it is suggested that fatigue in MS can predict the advent of other symptoms impacting the MS disease [25,26].

Despite the presence of studies concerning to walking-related motor fatigue in MS [8,23,24], the difference in other outcomes, such as mobility, walking capacity and cognitive

processing speed between groups differing in motor fatigue based on 6MWT were not investigated. Once the MS disease causes marked impairment in both motor and cognitive function, and these had been related to fatigue in people with MS, the aim of this exploratory study is to identify differences in mobility, walking capacity and cognitive function between groups of people with MS differing in walking-related motor fatigue, controlling for demographics and disease characteristics.

2. Patients and Methods

Part of the data for this exploratory study were collected during the project for the Validation of Brazilian version of the Patient-Determined Disease Steps (PDDS) scale [27].

2.1 Patients

This study involved data from a convenience sample of 58 persons with MS. We obtained the written informed consent prior to procedures and the Ethics Committee from the Department of Health/Federal District - Brazil approved this project, with the protocol number: 67098217.5.0000.5553. Inclusion criteria were (*1*) aged 18 years or older; (*2*) diagnosis of MS by experienced neurologist according to McDonald criteria [28]; (*3*) ambulatory with or without support. Exclusion criteria were (*1*) unable to understand the motor tests commands; (*2*) relapse over the past 90 days; and (*3*) other neurologic conditions in addition to MS.

2.2 Clinical and outcome measures

Participants underwent a neurological examination to obtain EDSS (Expanded Disability Status Scale) scores by a neurologist responsible for the MS outpatient clinic at the hospital, with extensive experience (> 15 years) with the disease and EDSS application. In addition, the patients scored the PDDS.

Participants then completed the symbol digit modalities test (SDMT) to assess cognitive processing speed, which has been a valid and reliable measure in MS patients [29]. The total correct score was recorded with higher scores indicating better cognitive function. Score from the oral modality was included in the analysis. Level of education was assessed by the number of years in formal education and categorized into tree levels: level 1 $\leq$ 4 years; level 2 $\leq$ 14 years; level 3 $\geq$ 15 years. The SDMT was administrated by a neuropsychologist.

Mobility was evaluated through the Time Up and Go (TUG) test. The starting point was determined after the subject had been seated in a standard height chair with their back flush

against the chair and their arms crossed in the chest. The patient was then instructed to stand up, walk 3 meters, turn around, walk back to the chair and sit down again. Timing began when the individual started to rise and ended when she/he returned to the chair and sat down [30,31]. The patients performed the test twice and the time in seconds was measured by a stopwatch.

To measure the short walk capacity, the MS Functional Composite guidelines were used for delivering the Timed 25-Foot Walk test (T25FW) [32]. Subjects were instructed 'to walk at fastest but safe speed' over a 25-foot/7.62-metre course. A static start was implemented and the timing, through a handheld stopwatch, started when the lead foot crossed the start line and stopped when the lead foot crossed the finish line. The patients performed the test twice.

Participants further completed the 6MWT 'at fastest speed, and to cover as much distance as possible'. The 6MWT was completed within a single corridor measuring ten-meter in length, with cones placed on opposite ends, while performing 180° turns around the cones [33]. The distance covered in each minute was measured. In order to identify fatigable and the non-fatigable people with MS, we measured the decline in distance walked by calculating the percentage change in distance walked – DWI [23]. The DWI was calculated using the following equation:

$$DWI = \frac{Distance\ walked\ at\ minute\ n - Distance\ walked\ at\ minute\ 1}{Distance\ walked\ at\ minute\ 1}\ x\ 100$$

Based on the DWI calculated between minutes 6 and 1 ($DWI_{6\text{-}1}$) a threshold of −15% was chosen to identify walking-related motor fatigue, $DWI_{6\text{-}1}$ [≤ −15%] (deceleration ≥ 15%).

Perceived fatigue was measured by the Borg scale (15 points). This scale starts on 6 (no exertion at all) and reach the number 20 (very, very hard - maximal effort). The perceived fatigue was asked in each minute of the 6MWT. The rate of change of the RPE over the 6MWT was calculated by the slope, which is the gradient of inclination of the RPE line.

Habitual physical activity was assessed by the Brazilian version [34] of the Baecke questionnaire [35]. This instrument quantifies structured exercise (sport index) as well as physical activity in leisure time (leisure time index) and at work (occupational index). Each index adopts values from 1 to 5, with 5 indicating the highest possible physical activity. The questionnaire asks for habitual physical activity and does not specify a delineated period of time. The total score was used for the analysis.

2.3 Statistical Analysis

The sample was divided into two groups. Those participants who presented deceleration ≥15% were classified with walking-related motor fatigue and allocated into the fatigable group. The remaining participants were allocated into the non-fatigable group. The Shapiro-Wilk test examined the normality of the data. Distribution of data was also visually checked with box-plots, q-q-plots, histograms and dot-plots. For comparisons between the fatigable and the non-fatigable groups, the student's *t*-test for independent samples was performed on the data regarding time since diagnostic. The Mann-Whitney test was executed on the remaining clinical and demographic data, including the RPE in arbitrary units, RPE slope and the $DWI_{6\text{-}1}$. Concerning to 6MWT, TUG, T25FW and habitual physical activity, potential confounding factors were accounted for including age, weight and time since diagnosis. Differences between groups were verified using an ANOVA with confounding factors (ANCOVA). For the SDMT, the level of education was inserted in the ANCOVA after a regression model identifying it as a co-variable. A p-value < 0.05 was considered statistically significant. All data analyses were performed using the SPSS program (SPSS 25.0, SPSS Inc., USA).

3. Results

Clinical and demographic characteristics from 58 participants diagnosed with relapsing-remitting MS (RRMS) are presented in table 1. No significant differences between fatigable and non-fatigable groups were identified regarding age and weight. Statistical significances were identified for EDSS [U=146.0; p<0.0001], PDDS [U=181.5; p=0.0003], and time since diagnosis with mean difference of 3.01 (95% CI: 0.06, 5.97) [t=2.05(51); p=0.045]. The subjective fatigue measured by the RPE in arbitrary units after the sixth minute of the 6MWT presented statistical difference between fatigable and non-fatigable people with MS [U=223.5; p=0.004]. The rate of change over de 6MWT calculated by the RPE slope did not show any statistical difference between groups [U=331.5; p=0.26], suggesting that both groups had similar increase in perceived exertion. Table 1 also provides the prevalence of the therapeutic strategies for the treatment of MS.

Table 1. Demographic characteristics and clinical outcomes of people with MS classified as fatigable and non-fatigable according to the DWI threshold (≤ -15%).

Variables	**Fatigable (n=23)**	**Non-Fatigable (n=35)**
Sex (F/M)	18/5	22/13
Age, y, median (IQR)	37 (34 - 46)	36 (26 - 46)
Weight, Kg, mean (SD)	76.9 (28.6)	68.8 (15.1)
EDSS, median (IQR)	4.5 (2.5 - 6.0) *	1.5 (1.0 - 2.5)
PDDS, median (IQR)	3 (1 - 4) *	0 (0 - 2)
Time since diagnosis, y, mean (SD)	9.35 (6.1) *	6.33 (4.4)
Therapeutic strategies	31% IMd | 68% IMs	45% IMd | 48% IMs
Education level, score (range)	2 (1 - 3)	2 (1 - 3)
RPE, arbitrary, median (IQR)	16 (14 - 20) *	12 (10 - 16)
RPE, slope, median (IQR)	0.74 (0.28 - 1.14)	0.34 (0.0 - 0.80)

Abbreviations: F, female; M, male; IQR, interquartile range; SD, standard deviation; EDSS, Expanded Disability Status Scale. PDDS, Patient Determined Disease Step. IMd, immunomodulators. IMs, immunosuppressants. RPE, rate of perceived exertion. * Denotes significant differences between fatigable and non-fatigable patients.

Figure 1 illustrates the DWI (%) in each minute of the 6MWT. The DWI_{6-1} was used to classify fatigable and non-fatigable patients with MS. Statistical significance was found between groups regarding the DWI_{6-1} [U=0.000; p<0.0001].

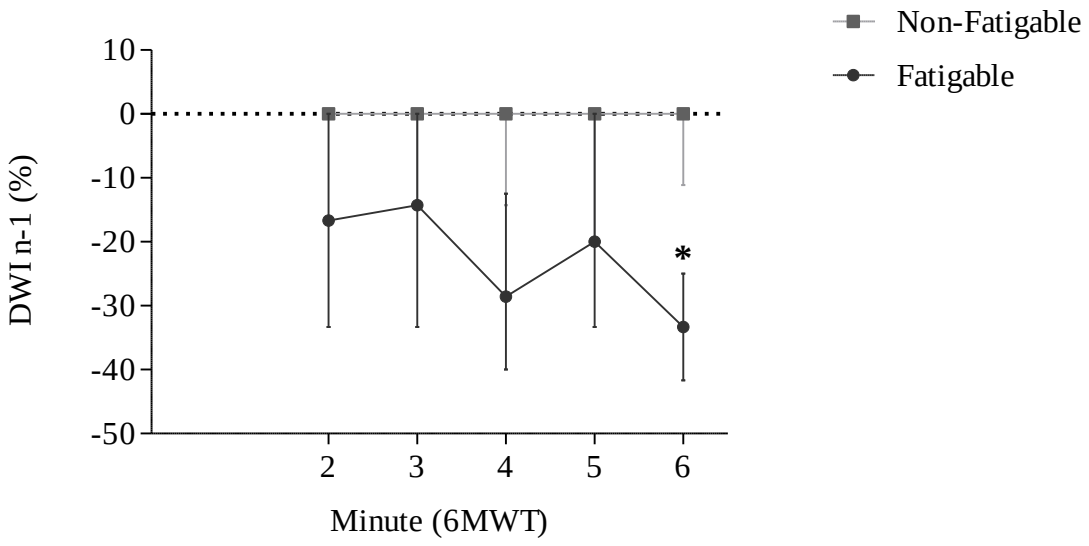

Figure 1. DWI (%) in each minute of the 6MWT. Data are presented as median and interquartile range. * Denotes statistical difference between fatigable and non-fatigable people with MS.

After adjusting for age, weight and time since diagnostic, the distance walked in the 6MWT revealed a mean difference of 161.50 (95% CI: 117.45, 205.54) between non-fatigable and fatigable people with MS [F (1,45) = 54.55, p<0.0001], see figure 2. Data from mobility and short walk capacity are also presented in figure 2. The time to perform the TUG test presented statistical difference between groups with mean difference of -5.26 (95% CI: -7.75, -2.78) [F (1,45) = 18.29, p<0.0001]. The velocity during the T25FW were also different between non-fatigable and fatigable people with MS presenting mean difference of 0.54 (95% CI: 0.34, 0.74) [F (1,45) = 30.28, p<0.0001].

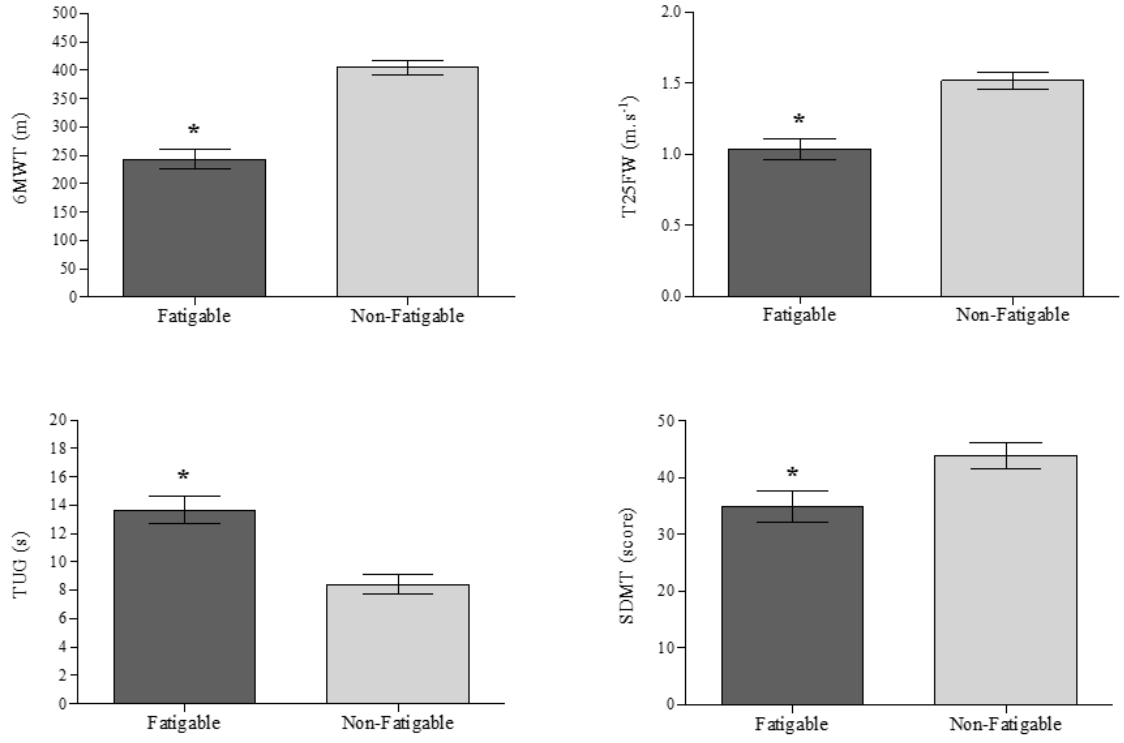

Figure 2. Difference between fatigable and non-fatigable people with MS in total distance for the six-minute walk test (6MWT), velocity during the timed 25-foot walk (T25FW) and time to perform the timed up and go (TUG) after adjusting for age, weight and time since diagnostic. The difference in the total score for the Symbol digit modality test (SDMT) were calculated after adjusting for level of education. Data are presented as estimated mean and standard error. * Denotes statistical significance between groups.

Level of education was a significant co-variate for cognitive processing speed, evaluated by the SDMT (b=11.55, β=0.52, p<0.001, R^2=0.25). After adjusting for education, there was a

mean difference of 8.95 (95% CI: 1.55, 16.35) in the SDMT scores [F (1,41) = 5.98, p=0.019] between non-fatigable and fatigable people with MS (see figure 2).

Regarding physical activity level, the total score was calculated and included in the analysis. No difference was observed between non-fatigable and fatigable people with MS with mean difference of -0.41 (95% CI: -1.22, 0.39) [F (1,40) = 1.08, p=0.305].

4. Discussion

The present study used a direct criterion to classify fatigable and non-fatigable people with MS regarding walking-related motor fatigue. By calculating the DWI and adopting a decline of more than 15% in the $DWI_{6\text{-}1}$ as a threshold, the prevalence of walking-related motor fatigue was 39.6% in our sample of MS patients. The fatigable people with MS presented significantly lower mobility, walking capacity and cognitive function compared to the less fatigable people with MS.

As reported by previous studies [8,23], the current work demonstrated that patients presenting motor fatigability were classified with higher disability level (EDSS score). Furthermore, a previous study [36] demonstrated that a linear decline in walking speed, calculated by the distance covered in each minute of the 6MWT, was significantly pronounced in patients with moderate MS degree (EDSS >3.5) when compared to healthy controls. These findings indicate that deceleration during the 6MWT, and, consequently, the walking-related motor fatigue, represents a clinically relevant feature of advancing disease in MS.

The present study corroborates with the findings from Leone et al [23], which showed decline in walking velocity through the 6MWT and a significant deceleration at minute six for those people with MS classified with walking-related motor fatigue ($DWI_{6\text{-}1} \leq -15\%$). Despite the complicated interpretation on underlying causes of deceleration in walking velocity, in a previous study from our group [24], we demonstrated that balance and knee flexor strength explained the declines in prolonged walking. Further, a recent study [37] also identified that static and dynamic balance, and maximal muscle strength from knee and ankle muscles, were significantly associated with gait speed from short walking tests and distance from the 6MWT. In addition to factors such as strength and balance, central mechanisms are also associated with exercise regulation and fatigue symptoms [25]. In MS patients, submaximal fatiguing exercise had been associated with an enhanced central motor drive and increased perception of effort [38]. During self-paced exercise, an optimal performance requires an increase in the RPE,

which ensures that a maximal tolerable RPE is reached at the moment exercise is completed, but not before. If the maximum RPE occurs before the end point, premature fatigue can adversely affect the completion of the task [39] . Results from this current study revealed that fatigable people with MS, classified by an objective threshold, reported higher arbitrary values of perception of effort after the 6MWT. However, as shown by the RPE slope (minute by minute), the increment in subjective fatigue did not differ between the fatigable and non-fatigable groups, suggesting a control of the exercise performance in accordance with the subjective fatigue. It seems that, in order to prevent a premature fatigue, the fatigable people with MS altered the pacing during the 6MWT slowing down the velocity reaching more than 15% of deceleration. Many models developed to the regulation of exercise intensity [40–43] indicate that afferent sensory feedback from various physiological systems is received and regulated by the brain in addition to other factors such as knowledge of task duration, memory of past similar experiences and motivation. This could explain the effect of strength and balance impairment on declines in prolonged walking [24], and, diminished cardiorespiratory capacity [44] and procession speed [20] in fatigued patients.

The present study supports the evidence of lower mobility and walking capacity impairment in the fatigable group compared to the non-fatigable. Mobility evaluated by the TUG test promotes the measurement of muscle function, balance, agility and coordination components [44]. The T25FW and the 6MWT evaluate walking by the velocity and endurance capacities, and have been related to lower muscle strength [14,45], balance [24,37], cardiorespiratory function [44]. A multicenter study from Dalgas et al [18] found a weak, but significant, negative relationship between subjective perception of physical fatigue (MFIS $_{physical}$) and walking velocity in people with MS. They also found that the TUG test showed a weak but significant relationship to the general perception of impact of fatigue. However, the present study reports mobility and walking impairments in fatigable people with MS classified with a threshold of walking-related motor fatigue, which may suggest a deterioration in coordination, dynamic balance, muscle function and agility of those patients.

Despite the occurrence of study supporting the concept that fatigue in MS patients is associated with discrete cognitive impairment [20], studies have failed to find a relationship between self-reported fatigue and cognitive impairment in people with MS [46,47]. The current study used a motor fatigue index to identify fatigable people with MS, which led to the detection of not only motor incapacities, but further cognitive impairment. Even after adjusting for level of education, which impacts cognitive scores [48], the fatigable patients performed significantly

lower score in the oral version of the SDMT. Concerning to cognitive function and motor control, the paradigm of cognitive-motor interference has been investigated [15]. Studies suggest that the slowing down in walking speed, especially during a cognitive-motor task, could be due by the interference of areas associated to executive functions, such as the pre-frontal and cingulate cortex, on the brain areas responsible for gait control [17,49]. In addition, abnormalities in the activation time between different motor connections and executive functions has been reported in people with MS who present fatigue symptoms [50,51].

Although the level of habitual physical activity had been measured by a valid questionnaire, the results showed no significant difference between fatigable and non-fatigable people with MS. A recent review from Motl et al. [52] presented studies revealing that accelerometry-measured sedentary behaviour was significantly associated with walking endurance and walking speed in people with MS. On the other hand, aerobic fitness, fatigue, fall risk and cognitive function, were not statistically associated with the overall volume of sedentary behaviour. The use of psychometric properties of physical activity measures, as well as of sedentary behaviour, have gained attention from researchers to identify modifiable factors that could predict MS symptoms [53,54]. In this context, the use of a more accurate measure of physical activity is suggested in order to investigate the effect of mobility, walking and cognitive impairment on the level of physical activity. In addition to rehabilitation and exercise programs, future researches are needed focusing on interventions that improve motor control and cognitive function, increase lifestyle physical activity, and perhaps modifying fatigue symptoms in people with MS.

The results from the current study confirm that the threshold of 15% of deceleration ($DWI_{6\text{-}1} \leq$ - 15%), proposed by Leone et al [23], to identify people with MS showing walking-related motor fatigue during the 6MWT was a valid index for our sample. In addition, the walking-related motor fatigue was accompanied by mobility, walking and cognitive impairments, suggesting the importance of such index and threshold in identifying others symptoms present in fatigable people with MS. This is supported by previous statement suggesting that fatigue in MS could predict the advent of symptoms related to the disease progression [25].

The DWI is an easy approach for clinical practice. The MS disease causes marked impairment in both motor and cognitive function and the evaluation of walking-related motor fatigue is important to consider, since it affects the activities of daily living and independence

of people with MS. From our knowledge, this is the first study evaluating motor fatigue and showing differences in others outcomes, such as mobility, walking capacity and cognitive function between people with MS differing in walking-related motor fatigue. Yet, our study presents some limitations: all of the MS patients were diagnosed with RRMS; the level of physical activity was measured by a subjective tool; the side effects of the different types of drugs used for the MS treatment were not discussed.

5. Conclusion

The direct DWI threshold [≤ -15%] was able to identify 39.6% of the MS patients presenting walking-related motor fatigue. Even adjusting for age, weight, time since diagnostic and level of education, fatigable people with MS presented mobility, walking capacity and cognitive function impairments compared to the non-fatigable patients. The level of disability was significantly higher for the fatigable group. Future studies may consider the impact of interventions targeting strength, balance control, gross motor coordination and, or cognitive processing speed in order to decrease motor fatigue.

Conflict of interest: The authors report no conflict of interest.

Acknowledgements: This study was supported in part by the Coordination for the Improvement of Higher Education (CAPES, Brazil – Finance Code 001).

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3.4 Artigo 4

Original article

IMPLICATIONS OF LOWER EXTREMITY MUSCLE POWER AND FORCE FOR WALKING AND FATIGABILITY IN MULTIPLE SCLEROSIS

Running title: Implication of power for physical function in MS

Cintia Ramari* 1, Lars G. Hvid* 2, Ulrik Dalgas 2, Ana R. Diniz 3, Felipe von Glehn 4, Ana C. de David 1

1 Faculty of Physical Education, University of Brasília, Brasília, Brazil

2 Exercise Biology, Department of Public Health, Aarhus University, Aarhus, Denmark

3 Faculty of Ceilândia, University of Brasília, Brasília, Brazil

4 Faculty of Medicine, University of Brasília, Brasília, Brazil

* these authors contributed equally to the work

Abstract

Background: Limitations in physical function are common in Multiple Sclerosis (MS). In MS, is not clear how muscle power implicates physical function and, its contribution to walking-fatigability.

Objectives: to investigate, (1) deficits in lower extremity muscle power (and force) and in walking in people with MS (pwMS); (2) associations between muscle power and physical functions; (3) whether the decrease in muscle power induced by walking contributes to walking-fatigability.

Methods: To measure muscle power (and force), 30 people with relapse-remitting MS and 28 healthy control (HC) performed the chair rise and plantar flexion tests on a force platform before and after a walking protocol. The walking protocol was composed of six 2-minute walks with rests of 30 seconds (12-minute walking). The GaitRite measured walking speed. Distance Walk Index (DWI%) was calculated. PwMS were allocated according to walking-fatigability and disability level.

Results: Higher deficit in muscle power compared to force was observed in pwMS vs. HC, particularly in pwMS having disability (PDDS score ≥ 1). Muscle power and force were associated with walking capacity, PDDS and subjective fatigue, but not with DWI%.

Conclusions: Deficits in lower extremity muscle power concomitant with deficits in walking capacity were found in pwMS. Walking-fatigability was accompanied by reductions in walking speed and, partially, in muscle power and force (i.e., delta%).

Keywords: Multiple Sclerosis; Functional Capacity; Fatigue; Muscle Function; Walking; Disability.

1 Introduction

A pathological hallmark of multiple sclerosis (MS) is the accumulation of demyelinating lesions in the central nervous system [1]. The bursts of focal inflammation, axonal loss and neurodegeneration are known as predominant causes of disability [2]. Common limitations in physical function in MS include the decrement in walking speed and endurance

[3–5], along with an increase in the time to perform stair climbing and chair rise [6–8]. These are partly driven by an inability of the neuromuscular system to perform rapid limb movements due to insufficient volitional drive to a given muscle [9,10], along with reduced rate of force development (RFD; force or torque production within a very short time window) [9]. Indeed, marked deficits have been observed in the lower extremity muscle strength and RFD in pwMS vs. healthy controls (HC) [11]. Moreover, systematic reviews have shown clear associations between lower extremity strength/RFD of different muscle groups and lower limb functional capacity such as walking and sit-to-stand [6,7,12]. While the vast majority of the studies have examined lower extremity strength/RFD during isometric or dynamic muscle contractions at fixed slow-to-moderate velocities, few examined muscle power (i.e., force multiplied by velocity) [13,14]. In MS, there is a lack of information regarding muscle power, particularly when derived from functional weight-bearing tasks, and more importantly how muscle power implicates physical function in pwMS. In aging studies, there is evidence that lower extremity muscle power compared to muscle strength is a stronger predictor of physical function - impacting mobility [15] and the ability to avoid falling during walking [16].

Fatigue is another consequence of the MS disease and is frequently reported by pwMS [17]. It can be defined as perceived fatigue (subjective sensations of weariness) [18] and as motor fatigue or fatigability (absolute or relative change in performance over a period of time during or after a given task [18]). Importantly, fatigability is known to be associated with baseline lower extremity muscle strength [19]. However, no studies have so far examined whether decrement in muscle power induced by a fatiguing task contribute to walking fatigability.

The aims of this cross-sectional study were (1) to investigate and characterize the deficit in lower extremity muscle power (and force) measured during unrestricted movement/motor tasks on a force platform, as well as in walking capacity in pwMS vs. HC, Fatigable vs. Non-Fatigable pwMS, and Low vs. High disability pwMS; (2) to verify associations between muscle power (and force) and walking capacity, disability level and physical subjective fatigue; (3) to investigate if there is a decrement in muscle power (and force) induced by a walking protocol, and its contribution to walking-fatigability. We hypothesized that pwMS would present deficit in lower extremity muscle power/force (preferentially in power) and in walking capacity, furthermore being specifically affected in Fatigable and High disability pwMS. Also, we hypothesized that muscle power/force would decrease after the walking-fatigability protocol contributing to fatigability and walking speed deterioration.

2 Materials and methods

2.1 Participants

A sample of thirty-four people with MS were recruited from private neurological clinics and via a MS community organization, via email and newsletter advertisements. Participants were eligible if they had a confirmed diagnosis of relapse-remitting MS (RRMS) according to the revised McDonald criteria [20]. Participants were excluded if they had a confirmed exacerbation or relapse of MS in the month prior to testing; had significant cardiac or respiratory disease, which could pose a risk when performing the walking protocol; if they could not walk for two minutes without stopping. Twenty-eight healthy controls (HC) matched for age (acceptable range of ± 2 y), sex, height (acceptable range of ± 5 cm) and weight (acceptable range of ± 5 kg) were recruited from the university staff and from the patients' known people.

2.2 Clinical evaluations

Initially, participants were asked to determine their disability level according to walking function using the Brazilian Patient Determined Disease Step scale (PDDS-BR) [21]. The Modified Fatigue Impact Scale (MFIS) (21-item questionnaire) was used to measure fatigue impact [22]. Given to the best previously reported association between physical function and the MFIS physical subscore [23], it was a priori decided to use this for the association analysis.

2.3 Force platform measures

Measures of power (and force) during the chair rise and the plantar flexion tests were collected before and after the walking protocol. Ground reaction force was measured using an AMTI force platform (AMTI, Watertown, MA). Vicon Nexus software - v2.8 (Vicon, Oxford, UK) was used to acquire data on kinetics at a sample rate of 1000 Hz. Data processing was performed using personalized MATLAB scripts (R2015a, The Mathworks, Natick, Massachusetts, USA). Signals were filtered digitally with a 10-Hz low-pass Butterworth filter (4th order) with zero phase lag [24].

Participants were instructed to begin the chair rise from a seated position on a standard wooden chair measuring 42 cm of height, with back support and no armrests, positioned adjacent to the force platform. With their feet at a comfortable self-selected width within the boundaries of the platform, the participants were instructed to cross their arms over the chest

and to rise and seat with a self-paced and comfortable speed, performing sequentially five chair rises without rest [24].

The plantar flexion consisted of five bilateral plantar flexions (heel rises) on a force platform. Participants were instructed to rise to the tip of their toes with the feet at a comfortable position as fast as possible, keeping the knees straight, the arms crossed on the chest and trying to keep on their tiptoe for at least one second before go down [25].

2.4 Walking protocol

Participants were instructed to walk along a 10-meter corridor, turning 180 degrees, for 2-minutes. The complete protocol was composed of six 2-minute walks with a rest period of 30 seconds between bouts, adding up to a total of 12 minutes of walking. Participants were instructed to "walk as fast as possible, but safely". If necessary, the use of a walking aid was allowed. Before, during the rest periods and after the last 2-minute walk, the maximal walking speed was assessed using a 4.88-meter GaitRite electronic walkway (CIR Systems Inc., Haverton, Pennsylvania, USA). Figure 1 presents the experimental protocol.

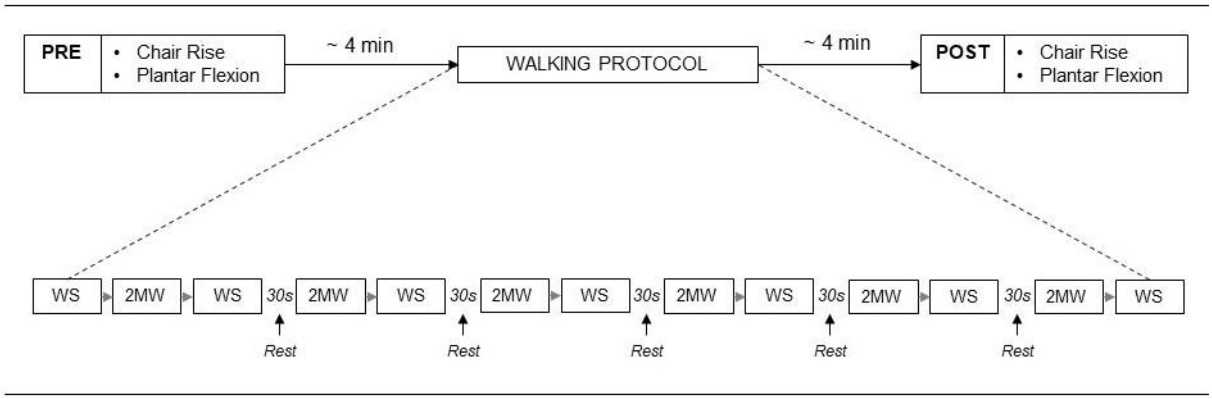

Figure 1. Experimental protocol. WS, walking speed. 2MW, 2-minute walk.

2.5 Data processing

Participant's body mass was assessed during quiet stance immediately before the trials. The ground reaction force (Fz) was normalized relatively to the body weight. The chair rise movement began with a relief phase and ended when Fz was equal to 1 - when the subject was standing [24,26]. We have not included the preparation phase in the analysis and we chose to analyse the chair rise from the first moment when the body weight was reached (Fz ~ 1, before the peak force) until the standing position (figure 2, A) [26]. For the plantar flexion, the Fz was

equal to 1 at the beginning of the movement, followed by an increase on Fz - reaching the peak force, and a rebound force event following the peak force. The end of the plantar flexion was defined when the Fz was around 1 after the rebound force event (figure 2, B).

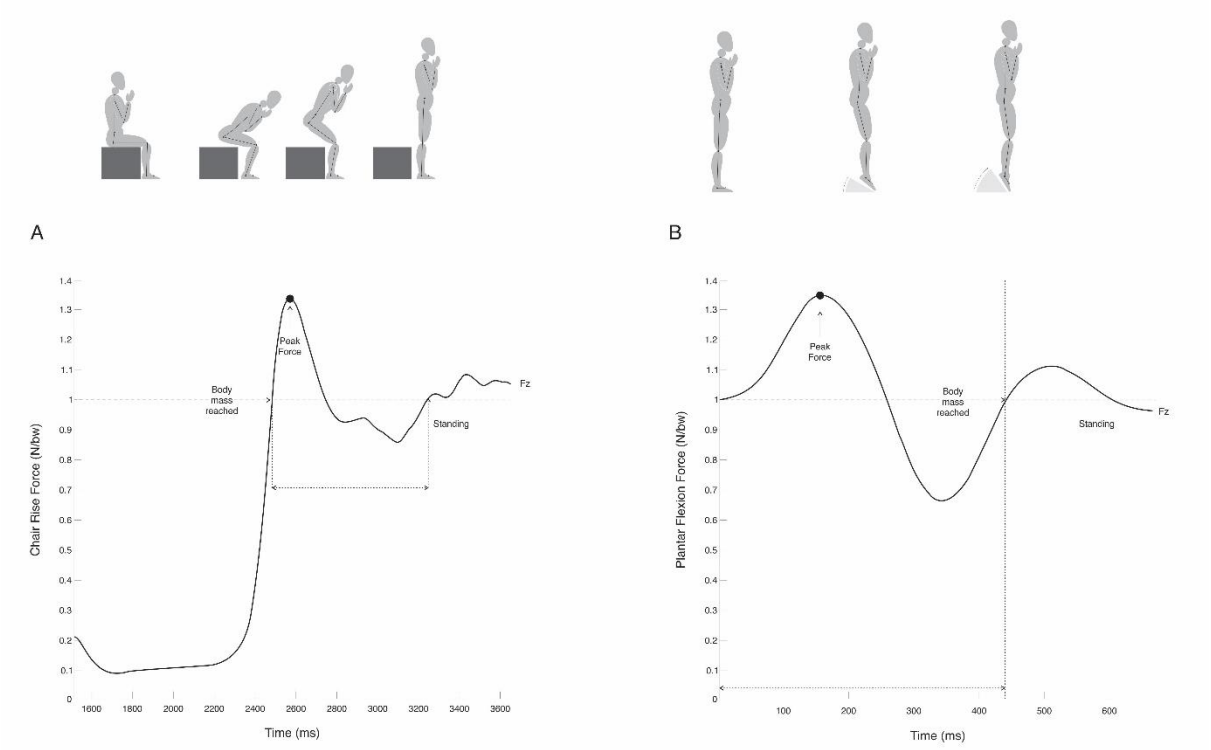

Figure 2. Individual data from a MS participant with mild disability (PDDS = 0) during the chair rise (A) and the plantar flexion (B) performance. The grey dotted line indicate the normalized body mass (=1). Non-dotted arrows indicate the events when the body mass and the peak force were reached. The black dotted two-sides arrows and the black dotted lines indicate the force-time curve interval used to extract force and power parameters.

Regarding to the Fz parameters, figure 2 presents the interval from the force-time curve chosen to extract force and calculate power. The peak force normalized per body weight (N/bw - Newton per body weight) was used in the analysis. To calculate power, the velocity-time curve was obtained by dividing the resultant force-time curve by the participant's body mass to find the acceleration-time curve. The acceleration was then numerically integrated with respect to time using the trapezoid rule, and the instantaneous power was calculated as the product of the force and velocity [27]. The normalized peak power (W/bw - Watts per body weight) was used in the analysis.

2.6 Statistical analysis

In order to investigate fatigability during walking, the Distance Walk Index (DWI) [28] was calculated based on the total distances walked during the first and at the last 2-minute walks. Adopting a cut-point of 10% of deceleration, DWI [≤ -10] [29], pwMS were allocated into two groups: MS Fatigable and MS Non-Fatigable. In addition, another subgroup classification was also adopted for pwMS according to the disability level, based on the PDDS score. Those with PDDS equal to zero were included in the PDDS Low group, while the remaining participants with PDDS ≥ 1 were included in the PDDS High group.

Statistical analyses were performed using linear mixed model in Stata version 14.2 (StataCorp LP, Texas, USA). Distribution of data was visually checked by box-plots, q-q-plots, histograms and dot-plots, showing that all the data were normally distributed, except for the plantar flexion force which was subsequently transformed prior to analysis: (1/plantar flexion) ^2). All baseline data were analysed with Group (HC and MS All; HC, MS Non-Fatigable and MS Fatigable; HC, PDDS Low and PDDS High) as a fixed effect and Participant ID as a random effect. Deficit scores were also calculated as the mean (95% confidence interval, CI 95%) percentage difference for pwMS in relation to the mean value from HC. Simple regression was carried out to examine potential associations between outcomes at baseline and pre-post the walking protocol (see Supplementary data for the latter). Data are presented as mean (CI 95%) unless otherwise stated. The effects of the walking protocol on muscle power/force and walking speed were analysed with Group (HC and MS All; HC, MS Non-Fatigable and MS Fatigable; HC, PDDS Low and PDDS High) and Time (Pre and Post) as fixed effects and Participant ID as a random effect. DWI was analysed with Group (HC and MS All; HC, MS Non-Fatigable and MS Fatigable; HC, PDDS Low and PDDS High) as a fixed effect and Participant ID as a random effect. Changes in force, power and walking speed were also calculated as the mean (CI 95%) percentage difference between pre and post (delta, □%) the walking protocol. Graphs were made using GraphPad Prism version 7.03 (GraphPad Software, California, USA). Level of statistical significance was set at $p < 0.05$.

3 Results

3.1 Baseline characteristics

Table 1 presents participant characteristics and clinical results. No differences were found regarding sex proportions, age, height, and weight between HC and pwMS. Subjective fatigue measured using the MFIS revealed that pwMS perceived to be more fatigued than HC. The MS Fatigable group presented a lower score for the MFIS total and a higher score for the

MFIS physical, when compared to the Non-Fatigable group. MFIS total and all subscores were significantly higher for the PDDS High group compared to PDDS Low and HC. As a measure of physical function, the total distance travelled during the walking protocol (12 minutes in total) was shown to be shorter for pwMS vs. HC, shorter in MS Fatigable vs. MS Non-Fatigable, and shorter in PDDS High vs. PDDS Low. In general, the DWI revealed that pwMS presented higher walking-induced fatigability compared to HC, but this was due to the MS Fatigable group (as no difference was observed between Non-Fatigable and HC). In addition, DWI was not impacted by the disability level, and no differences could be found between PDDS Low and PDDS High groups.

Table 1. Participant characteristics of the total sample and clinical results.

	HC	MS All	MS Non-Fatigable	MS Fatigable	PDDS Low	PDDS High
n (females)	28 (22)	30 (24)	21 (18)	9 (6)	13 (11)	17 (13)
Age (y)	40.3 (35.9 : 44.6)	41.9 (37.7 : 46.1)	40.6 (36 : 45.2)	45 (34.6 : 55.4)	39.8 (32.8 : 46.9)	43.5 (37.9 : 49.1)
Height (m)	1.66 (1.62 : 1.70)	1.65 (1.61 : 1.69)	1.63 (1.59 : 1.67)	1.70 (1.61 : 1.78) ***b***	1.64 (1.59 : 1.69)	1.66 (1.60 : 1.71)
Weight (kg)	67.6 (62.05 : 73.31)	68.37 (62.5 : 74.2)	63.9 (58.4 : 69.5)	78.6 (64.4 : 92.9) **a,b**	66.8 (57.2 : 76.4)	69.5 (61.3 : 77.6)
PDDS	---	1.23 (0.6 : 1.81)	1 (0.42 : 1.57)	1.77 (0.20 : 3.35)	0	2.1 (1.42 : 2.93) **c**
Time since diagnosis (yrs)	---	7.7 (5.3 : 10.1)	6.5 (4.2 : 8.8)	10.6 (4.05 :17.2) ***b***	6.8 (3.0 : 10.6)	8.4 (4.8 : 11.9)
MFIS total	24.6 (19.3 : 29.8)	39.1 (31.7 : 46.5) **a**	39.7 (30 : 49.4) **a**	37.7 (24.8 : 50.7) **a,b**	29.4 (18.1 : 40.8)	46.6 (37.5 : 55.6) **a,c**
MFIS cognitive	12.3 (9.3 : 15.2)	17.3 (13.6 : 20.9) **a**	18 (13.1 : 22.9) **a**	15.5 (9.6 : 21.4)	13.3 (7.2 : 19.4)	20.2 (15.7 : 24.8) **a,c**
MFIS physical	10.5 (7.9 : 13.1)	18.2 (14.9 : 21.4) **a**	17.9 (13.9 : 22) **a**	18.8 (12.1 : 25.6) **a,b**	13.5 (8.9 : 18.0)	21.8 (17.7 : 25.9) **a,c**
MFIS psychosocial	2.0 (1.3 : 2.7)	3.6 (2.7 : 4.5) **a**	3.7 (2.5 : 4.9) **a**	3.3 (1.5 : 5.1)	2.5 (1.2 : 3.8)	4.4 (3.2 : 5.7) **a,c**
Distance total, 12 min (m)	1156 (1102 : 1210)	898.3 (808.4 : 988.3) **a**	955.9 (867.1 : 1045) **a**	764.1 (538.3 : 989.9) **a,b**	1051 (985.5 : 1117) ***a***	781.4 (652.6 : 910.1) **a,c**
DWI (%)	-1 (-3 : 1)	-7 (-10 : -3) **a**	-1 (-3 : 1)	-19 (-25 : -13) **a,b**	-6 (-11 : -2) ***a***	-7 (-13 : -1) **a**

Results are presented as mean and 95% confidence interval (CI). PDDS, patient determined disease steps. MFIS, modified fatigue impact scale. DWI, distance walked index. Statistical significance ($p \leq 0.05$) and trends ($0.05 < p < 0.10$, shown in italic) are denoted by **a**: different from healthy controls (HC), **b**: different from Non-Fatigable persons with MS, and **c**: different from PDDS Low.

3.2 Deficit in lower extremity muscle power/force and walking capacity - comparisons of subgroups

As shown in figure 3A, pwMS presented greater limitation of walking capacity compared to HC. Also, lower extremity muscle force and preferentially muscle power were more impaired in pwMS compared to HC (corresponding to deficits of 5% in force and 15-20% in power). MS Fatigable and MS Non-Fatigable groups presented a greater deficit in total distance walked, walking speed and power from the plantar flexion when compared to the HC. A greater deficit in distance walked was found for Fatigable pwMS when compared to the Non-Fatigable. Deficits in force from plantar flexion and chair rise, and in chair rise power were only present in Non-Fatigable pwMS (figure 3B). The PDDS High group showed greater deficits in walking capacity and in muscle power (and force) when compared to HC (Figure 3C). In addition, compared to the PDDS Low group, the PDDS High group walked shorter and slower, presented greater deficit in power (and force) during chair rise. However, the PDDS Low group presented impaired walking capacity when compared to HC, although power (and force) were not deficient.

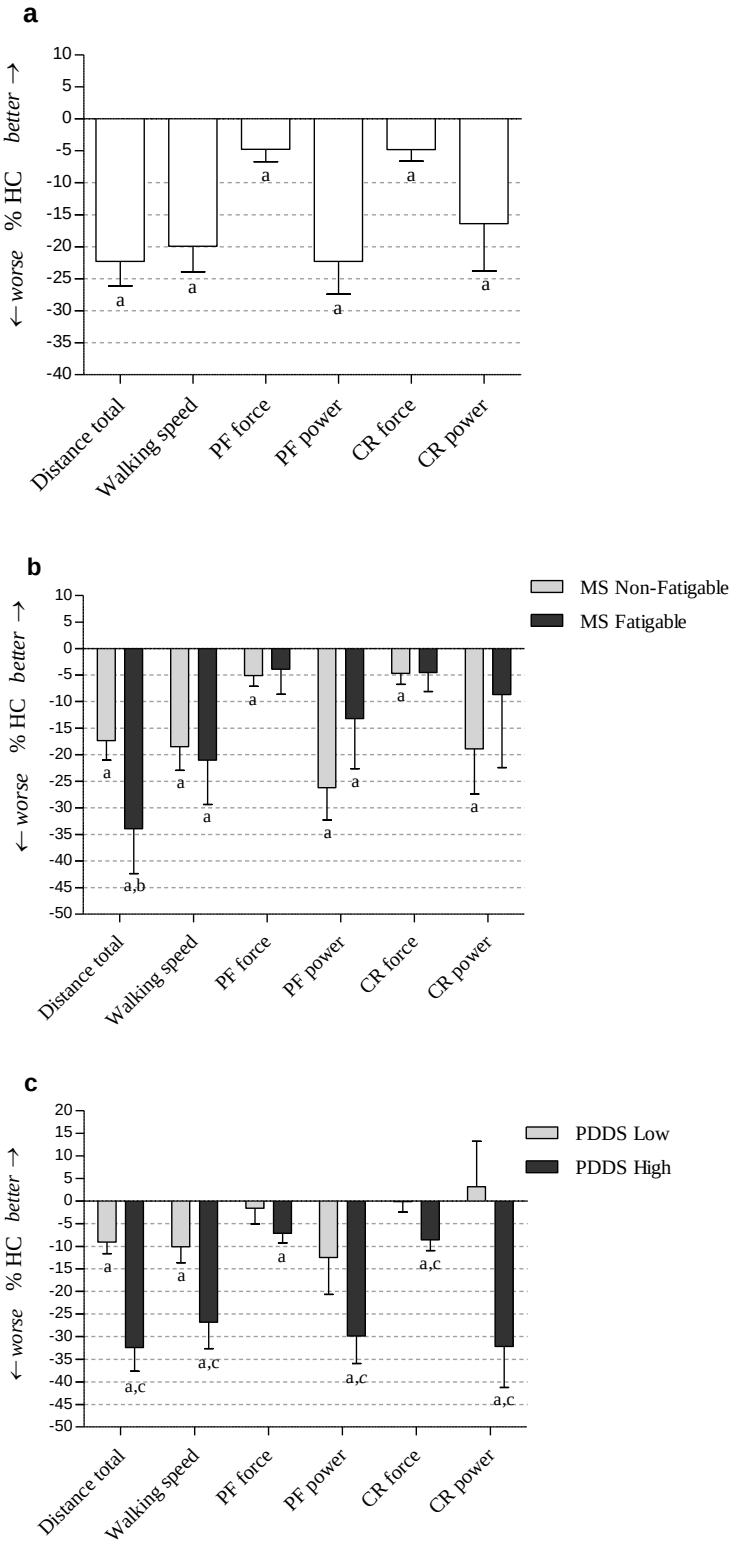

Figure 3. Deficit physical function regarding to walking capacity and lower extremity muscle force/power calculated as percentage of the mean values from the healthy control (HC) group. Results presented as mean and standard error. a, deficits presented for all the MS patients. b,

deficits presented for the Fatigable and the Non-Fatigable people with MS. c, deficits presented according to the PDDS score, Low (= 0) or High (≥ 1). PF, plantar flexion. CR, chair rise. Statistical significance ($p \leq 0.05$) and trends ($0.05 < p < 0.10$, shown in italic) are denoted by "a": different from healthy controls (HC), "b": different from Non-Fatigable persons with MS, and "c": different from PDDS Low.

3.3 Baseline associations between muscle power/force and walking capacity, disability level and physical subjective fatigue in pwMS

Associations were observed between lower extremity muscle power/force and walking speed/distance as well as disability level (PDDS) (Table 2). Muscle power explained 15 to 18% of the variance in walking speed, 20 to 27% of the variance in total distance travelled, 18 to 21% of the variance in the PDDS score, and 13 to 39% of the variance in the MFIS physical subscore. No associations were found between power/force and the DWI (%). Force from the chair rise explained a somewhat higher part of the variance in physical functions with values ranging from 25 to 43%, when compared to the plantar flexion values with values ranging from 11 to 25%. Figure 4 shows the associations between lower extremity muscle power/force and walking speed, also revealing a higher variability in power compared to the force values.

Table 2. Coefficients from the simple regression analysis including function, fatigability and perception of fatigue and force and power from the plantar flexion and chair rise in persons with MS.

	Plantar Flexion				Chair Rise			
	Power (W/bw)		Force (N/bw)		Power (W/bw)		Force (N/bw)	
	R^2	p-Value	R^2	p-Value	R^2	p-Value	R^2	p-Value
Walking speed (m/s)	0.18	0.019 [d]	0.25	0.005 [d]	0.15	0.038 [d]	0.33	0.001 [d]
Distance total, 12 min (m)	0.20	0.013 [d]	0.19	0.014 [d]	0.27	0.003 [d]	0.43	0.000 [d]
DWI (%)	0.05	0.197	0.00	0.865	0.00	0.866	0.01	0.557
PDDS	0.21	0.010 [d]	0.11	0.068 *[d]*	0.18	0.022 [d]	0.25	0.005 [d]
MFIS physical	0.13	0.048 [d]	0.14	0.035[d]	0.39	0.000 [d]	0.35	0.001 [d]

Abbreviations: DWI, distance walked index. PDDS, patient determined disease step. MFIS, modified fatigue impact scale. N/bw, Newton/body weight. W/bw, Watts/body weight. Statistical significance ($p \leq 0.05$) and trends ($0.05 < p < 0.10$, shown in italic) are denoted by d.

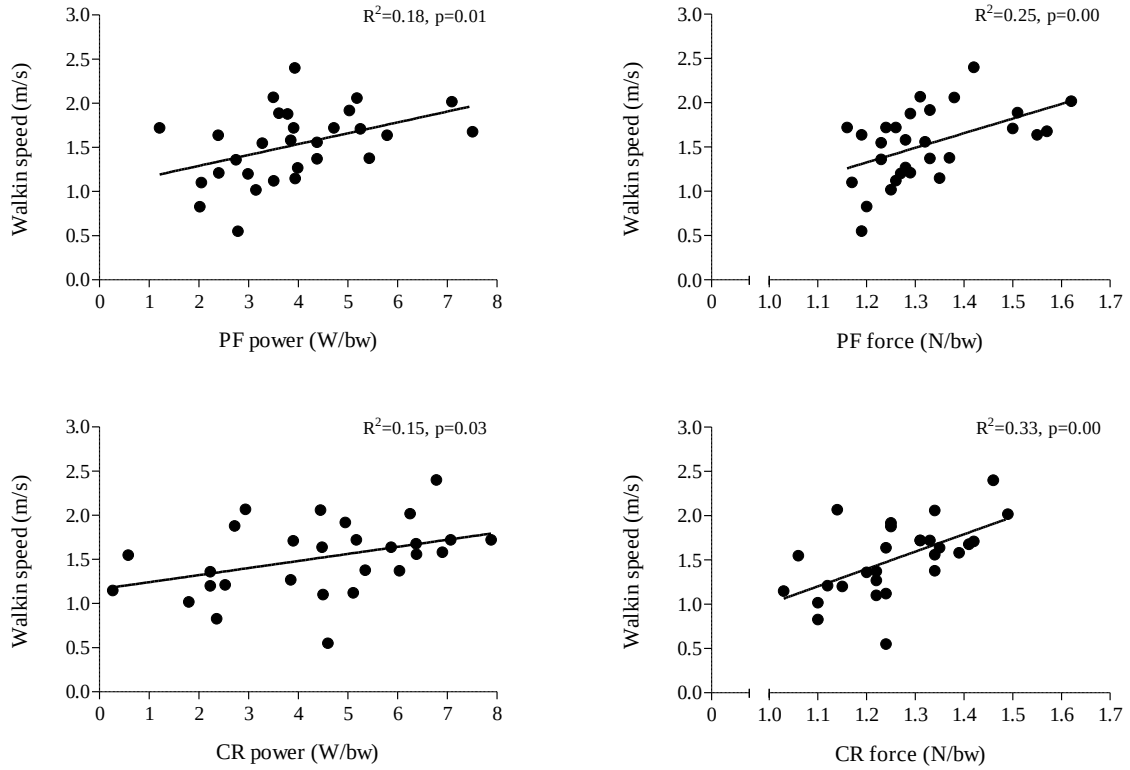

Figure 4. Associations between lower extremity muscle power/force from functional tasks - plantar flexion (PF) / chair rise (CR), and baseline walking speed.

3.4 Pre-post changes induced by the walking protocol - comparisons between subgroups

MS Fatigable presented trends towards delta changes (%) in power (and force) from chair rise compared to HC and to MS Non-Fatigable (see Table 3). No pre-post changes were found for the PDDS subgroups.

Regarding walking speed, pre-post change was only significant for the MS Fatigable group, with reduced walking speed after the walking protocol. In addition, a trend for significance was found for delta (%) between MS Fatigable and Non-Fatigable.

Table 3. Lower extremity force/power and walking speed pre and post the walking-fatigability protocol.

		HC	MS All	MS Non-Fatigable	MS Fatigable	PDDS Low	PDDS High
Plantar Flexion							
Force (N/bw)	pre	1.40 (1.35 : 1.45)	1.33 (1.28 : 1.39) **a**	1.33 (1.27 : 1.39) **a**	1.34 (1.19 : 1.50)	1.38 (1.27 : 1.48)	1.30 (1.24 : 1.36) **a**
	post	1.39 (1.34 : 1.45)	1.35 (1.29 : 1.42)	1.34 (1.28 : 1.41)	1.37 (1.18 : 1.56)	1.42 (1.28 : 1.55)	1.31 (1.24 : 1.37)
	Δ %	*-0 (-3 : 2)*	*1 (-1 : 3)*	*0 (-2 : 4)*	*2 (-3 : 7)*	*2 (-1 : 5)*	*0 (-3 : 4)*
Power (W/bw)	pre	5.06 (4.48 : 5.65)	3.94 (3.40 : 4.47) **a**	4.02 (3.33 : 4.72) **a**	3.73 (2.82 : 4.65) **a**	4.43 (3.53 : 5.34)	3.55 (2.90 : 4.21) **a, *c***
	post	5.31 (4.63 : 5.99)	4.15 (3.63 : 4.67)	4.19 (3.55 : 4.83)	4.03 (2.91 : 5.16)	4.66 (4.09 : 5.22)	3.79 (3.01 : 4.58)
	Δ %	*5 (-3 : 13)*	*15 (-4 : 33)*	*15 (-11 : 41)*	*14 (-2 : 31)*	*22 (-20 : 65)*	*9 (-8 : 27)*
Chair Rise							
Force (N/bw)	pre	1.33 (1.29 : 1.37)	1.27 (1.22 : 1.32) **a**	1.27 (1.21 : 1.33) ***a***	1.26 (1.13 : 1.39)	1.33 (1.26 : 1.40)	1.22 (1.15 : 1.28) **a, c**
	post	1.36 (1.32 : 1.40)	1.28 (1.22 : 1.33)	1.29 (1.23 : 1.35)	1.24 (1.09 : 1.40)	1.34 (1.27 : 1.41)	1.23 (1.16 : 1.31)
	Δ %	*2 (0 : 4)*	*1 (-0 : 2)*	*2 (1 : 3)*	*-2 (-5 : 2)* ***a, b***	*1 (-2 : 3)*	*1 (-0 : 3)*
Power (W/bw)	pre	5.47 (4.52 : 6.43)	4.58 (3.75 : 5.41)	4.44 (3.46 : 5.41)	4.94 (2.92 : 6.96)	5.64 (4.44 : 6.85)	3.71 (2.65 : 4.77) **a, c**
	post	5.60 (4.80 : 6.41)	4.89 (3.92 :5.86)	4.89 (3.78 : 5.99)	4.35 (1.69 : 7.0)	5.96 (4.40 : 7.53)	3.84 (2.68 : 5.01)
	Δ %	*11 (-4 : 26)*	*14 (-12 : 41)*	*27 (-5 : 60)*	*-15 (-49 : 19)* ***b***	*6 (-9 : 22)*	*21 (-28 : 70)*
Gait Parameter							
Walking speed (m/s)	pre	1.90 (1.81 : 2.00)	1.52 (1.37 : 1.68) **a**	1.55 (1.37 : 1.73) **a**	1.45 (1.05 : 1.86) **a**	1.71 (1.56 : 1.86) ***a***	1.39 (1.15 : 1.63) **a, c**
	post	1.83 (1.71 : 1.94)	1.42 (1.25 : 1.60)	1.52 (1.30 : 1.74)	1.20 (0.88 : 1.52) **d**	1.58 (1.36 : 1.80)	1.30 (1.03 : 1.57)
	Δ %	*-4 (-8 : 1)*	*-4 (-17 : 10)*	*2 (-16 : 21)*	*-20 (-27 : -12)* ***b***	*-6 (-20 : 8)*	*-2 (-24 : 20)*

Results are presented as mean and 95% confidence interval (CI). Statistical significance ($p \leq 0.05$) and trends ($0.05 < p < 0.10$, shown in italic) are denoted by **a**: different from healthy controls (HC), **b**: different from MS Non-Fatigable, **c**: different from PDDS Low, and **d**: different from Pre (within same group).

4 Discussion

The main findings of the present study were that: (1) more pronounced deficit in lower extremity muscle power vs. muscle force was observed in pwMS compared to HC, particularly in pwMS having higher disability (PDDS score ≥ 1); (2) lower extremity muscle power and force were (to a similar extent) associated with walking capacity, PDDS score and MFIS physical (power R2=0.11-0.39 / force R2=0.11-0.43), whereas no association with DWI% was observed; (3) The present intermittent walking protocol did not impair lower extremity muscle power/force of pwMS and HC, despite inducing a decrement in walking speed and a trend to significance in the chair rise muscle power (and force) delta (%) in Fatigable pwMS.

4.1 Deficit in lower extremity muscle power/force and walking capacity - comparisons of subgroups

In general, pwMS presented approximately 20% of deficit in walking capacity in relation to HC, and our results thus corroborate with previous findings [5], both, for short distance [30] and long distance walking [4].

For all pwMS, deficit in muscle power (15-20%) were shown to be more prominent than deficit in muscle force (5%). According to a review by Jørgensen et al. [11], lower extremity muscle strength (isokinetic dynamometer assessment) presented a deficit of approximately 25% in pwMS compared to HC. In addition, only one study [13] could be found reporting a deficit of about 25% in the knee extensor muscle power in pwMS, while no deficit in power was found for the dorsiflexor muscle. The markedly lower deficit in force in our study is probably partly due to the tasks performed and to the method applied to extract power/force, using the GRF. In addition, most of the previous studies enrolled moderately impaired pwMS, whereas in the present study more well-functioning, mildly impaired pwMS were evaluated (i.e., only six participants presented PDDS ≥ 3). In a similar way, Cruz et al [31] have also found deficits in muscle force and RFD from the chair rise on a force platform in pwMS when compared to HC. While their study used RFD as a marker of muscle function deficiency – argued to be a strong functional correlate to tasks of daily living – the present study used peak power.

Analysis of subgroups revealed a substantial difference in walking endurance (i.e., total distance) in MS Fatigable when compared to the MS Non-Fatigable group, whereas baseline walking speed did not differ between groups. This is an interesting observation, as it suggests that different mechanisms are involved in determining walking performance (at rested

condition) and walking-induced fatigability. It furthermore emphasizes that assessment of fatigability should be highly prioritized when assessing pwMS suffering from fatigue. In contrast to our hypothesis, our results regarding lower extremity muscle power/force showed no difference in plantar flexion and chair rise power/force between Fatigable pwMS and HC. In addition, no significant differences were found between Fatigable and Non-Fatigable pwMS. This results could suggest that the DWI% was not affected by the baseline values of lower extremity muscle power/force in our sample (in the way we have assessed it, performing the tasks with a comfortable speed). While subjective fatigue has been only weakly associated to objective walking capacity [23], and inconsistent findings have shown a weak negative association with muscle strength [32], no studies have to our knowledge reported differences in walking speed and in lower extremity muscle power/force in Fatigable and Non-Fatigable pwMS defined by a direct fatigability method, such as the DWI.

Concerning to the disability level, walking capacity (endurance and speed) were already limited in the PDDS Low group when compared to HC. However, their deficit in lower extremity power/force did not differ from HC until PDDS increased to ≥1. Deficits in power was clearly more prominent and may reflect the slowing down in volitional neural drive [10], which is one of the main characteristics of the MS disease progression affecting disability. In addition, differences in muscle power/force between the PDDS Low and High groups were significant during the chair rise task but not during the plantar flexion. It suggests that a more complex dynamic task (i.e. chair rise) maybe required a more optimal motor control in order to synchronize different muscular groups [33] , and might be important in order to detect motor deficiency across the disability level in pwMS.

4.2 Baseline associations between muscle power/force and walking capacity, disability level and physical subjective fatigue in pwMS

Although the associations with plantar flexion power/force were statistically significant, our results suggest that a more complex task such as the chair rise explained a larger part of the variance in physical function and in subjective physical fatigue. Corroborating with findings from a review study from our research group [12], where lower limb muscle strength explained 20 to 30% of the variance across a number of lower-limb functional capacity tests, the current study showed that plantar flexion force explained about 19%-25%, while the chair rise force explained about 33%-43% of the variance in walking capacity. Despite the more pronounced

deficits in power vs. force when pwMS were compared to HC, force still explained a larger part of the variance in walking capacity.

An unexpected finding was the lack of association between power/force and the DWI%. As shown in a previous study [19], strength from the knee flexor muscles explained 27% of the variance in DWI% during the 6-minute walking test, which may be explained by the muscle strength evaluation, using an isolated knee flexor test [19]. In the present study, the GRF represented the resultant of multiple muscle groups, including muscles from the trunk and lower extremity, which could lead to compensations from stronger muscles. In addition, the lower limb functional tasks performed in our study could be classified as submaximal tasks, likely suggesting the need for a maximal muscular contraction at baseline in order to explain variance in walking fatigability.

4.3 Pre-post changes induced by the walking protocol - comparisons between subgroups

No difference in absolute lower extremity muscle power/force could be found between pre and post the walking protocol for pwMS and HC. However, the percentage delta score showed trend towards the Fatigable pwMS having a decreased chair rise force compared to HC and to the MS Non-Fatigable, and chair rise power when compared to the Non-Fatigable. When isolated leg muscle contractions were evaluated before and after the six-minute walk test, McLoughlin et al. [34] reported a decrement in absolute strength from the knee extensors and dorsiflexor muscles. However, the current study is the first to evaluate lower extremity muscle power/force using functional tasks after an intermittent walking protocol. In addition, the lack of changes induced by the proposed walking protocol on muscle power/force could be due to the long period (~4 min) taken to perform the post evaluation as well as by the intermittent characteristic of the protocol. This suggest that future studies should evaluate lower extremity muscle power/force during the protocol and immediately after completing the protocol, not allowing a long rest period in order to identify potential mechanisms related to fatigability.

For walking speed, when comparing the delta (%) between MS Fatigable and Non-Fatigable, a significant decrement in walking speed was found for the Fatigable group. Previous studies investigating the impact of the two and six -minute walk on spatiotemporal gait parameters have not found the slowing-down in walking speed after walking tests [35,36]. In addition, six-minute walking had induced an increment in walking speed (at a comfortable pace) and there was no effect of exertion in the fast walking speed [37]. Corroborating with these findings, no changes could be found in our sample when analysing all pwMS in the same group.

In addition, despite the lack of differences found in the baseline values of walking speed and lower extremity muscle power/force between Fatigable and Non-Fatigable pwMS, decrement in walking speed and muscle power/force delta (%) were found in the Fatigable pwMS. This suggest that Fatigable and Non-Fatigable pwMS presented similar baseline physical and muscle function, but these functions were altered after the walking protocol for Fatigable pwMS, explaining walking-fatigability. Thus, reinforcing the importance of a direct method such as the DWI to identify people presenting motor fatigability to investigate causalities related to fatigue in MS.

4.4 Limitations of the study

Although the current study is the first to evaluate and characterize lower extremity muscle power/force measured during dynamic functional tasks in pwMS, as well as to investigate the effects of an intermittent walking protocol on muscle power, it presents some limitations such as: (1) pwMS enrolled in this study were mostly well-functioning; (2) perhaps, the time taken to perform the evaluation post the walking protocol was long enough to promote muscle function recovery, preventing the detection of the effects of the walking-fatigability; (3) the dynamic functional tasks were performed with a comfortable and self-paced speed, which affected the absolute values of power and, possibly, diminishing the impact of muscle power on physical functions; (4) the cross-sectional designs, limit inference related to causality of impairment in lower extremity muscle power/force and fatigability.

5 Conclusions

The present study revealed substantial deficits in lower extremity muscle power (derived from chair rise and plantar flexion on a force plate) concomitant with deficits in walking capacity in pwMS vs. HC, Fatigable vs. Non-Fatigable pwMS, and Low vs. High disabled pwMS. Importantly, deficits in muscle power were greater than deficits in muscle force. Both muscle force and power were associated with walking capacity, but not with DWI%. Walking-fatigability induced by an intermittent 6 x 2-min walk bouts were accompanied by reductions in walking speed and, partially accompanied by reductions in lower extremity muscle force and power (i.e., delta%).

Declaration of interest

CR declares no conflict of interest.

LGH has received research support, travel grants, and/or teaching honoraria from Biogen and Sanofi Genzyme.

IB declares no conflict of interest.

U.D. has received research support, travel grants, and/or teaching honorary from Biogen Idec, Merck Serono, Novartis, Bayer Schering, and Sanofi Aventis as well as honoraria from serving on scientific advisory boards of Biogen Idec and Genzyme.

ARD declares no conflict of interest.

FG declares no conflict of interest.

ACD declares no conflict of interest.

Geolocation information

South America – Brazil; Europe – Denmark.

Acknowledgements

This work was partially funded by the Coordination for the Improvement of Higher Education (CAPES, Brazil – Finance Code 001).

We thank the neurologists Carlos Bernardo Tauil and Eber Castro Correa for the assistance with inviting the patients from their private clinics to participate in this study, and the Apemigos (Association of People with Multiple Sclerosis from the Federal District) for encouraging the participants to contribute with the multiple sclerosis research projects. At last, we thank all the participants.

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3.5 Artigo 5

Original Article

CHANGES IN SPATIOTEMPORAL GAIT PARAMETERS DEPEND ON THE MANIFESTATION OF PERFORMANCE FATIGABILITY IN PERSONS WITH MULTIPLE SCLEROSIS

Cintia Ramari a, Ana R. Diniz b, Felipe von Glehn c, Ana C. de David a,b

a Faculty of Physical Education, University of Brasília, Brasília, Brazil

b Faculty of Ceilândia, University of Brasília, Brasília, Brazil

c Faculty of Medicine, University of Brasília, Brasília, Brazil

ABSTRACT

Introduction: Walking is perceived as the most important bodily function for persons with multiple sclerosis (pwMS) and is impaired in more than 70% of pwMS. In addition, the effect of multiple sclerosis (MS) on gait pattern increases in fast walking and during fatiguing exercises, altering spatiotemporal gait parameters and walking reserve.

Objectives: To investigate the impact of an intermittent-walking protocol on gait pattern and on fatigability of pwMS and their association with state and trait fatigue.

Methods: Twenty-six persons with relapse-remitting MS and twenty-eight healthy controls (HC) were included in this study. The Modified Fatigue Impact Scale and the Symbol Digit Modality Test were used to evaluate trait fatigue and cognitive function, respectively. Participants walked six times during uninterrupted 2-minutes. Before, during the rest periods and after the last 2-minute walk, the rate of perceived exertion (RPE) was measured - Borg Scale, and the spatiotemporal gait parameters were assessed with the GaitRite. The cut-off of 10% of deceleration of the distance walked index classified pwMS into two groups: MS Fatigable (^{MS}-F) and MS Non-Fatigable (^{MS}-NF).

Results: PwMS walked slower, shorter distances and presented shorter step length compared to HC. No effects of the intermittent-walking protocol were found for all pwMS, but ^{MS} – F deteriorated walking speed, step length and cadence. Walking dysfunction was associated with perceived fatigability, trait fatigue, cognitive function and disease step. Trait fatigue was associated perceived fatigability but not with performance fatigability.

Conclusions: changes in spatiotemporal gait parameters and the manifestation of perceived and performance fatigability were found in pwMS. However, these were dependent on the manifestation of walking-related fatigability.

1. Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory disorder of the central nervous system (CNS) and a leading cause of disability in adults worldwide [1]. Clinically, persons with MS (pwMS) demonstrate a variety of neurological symptoms associated with neuroinflammation and degeneration of the CNS, with great impact on physical and mental functioning [2]. Concerning to physical function, walking is perceived as the most important bodily function for pwMS [3] and is impaired in more than 70% of the patients [2]. PwMS perform considerably worse on short- and long-distance walking tests such as the timed 25-foot walk (T25FW) and the six-minute walk test (6MWT) vs healthy controls (HC) [4]. In addition to factors such as impaired lower extremity muscle strength and balance that affect walking performance in pwMS [5,6], alterations in spatiotemporal gait parameters have been reported in this population. Compared to HC, pwMS usually walk with slower velocity, lower cadence, shorter step length, longer stride time, higher step width and spend more time in the double support. Furthermore, the effect of MS on gait pattern increases in fast walking conditions [7]. Walking speed reserve has also been investigated in pwMS and reflects the ability of increasing speed in response to different environmental demands [8]. However, walking reserve (WR) of the remaining spatiotemporal parameters have not yet been proposed for pwMS. Low walking speed reserve represents the incapacity of increasing walking speed, which could be due to the inability of increasing cadence and/or step length, suggesting that a person typically walks at, or close to, their maximal speed, even when necessary (e.g., in adverse circumstances such as crossing the street).

Another symptom that affects walking in pwMS is fatigue. Fatigue symptom is highly reported and present in about 70% of pwMS [9]. Fatigue in MS can be conceived as “trait fatigue” or “state fatigue”. Trait fatigue comprehend the pathological fatigue referring to a frequent, prolonged, or constant sensation over longer time frames, which represents the fatigue construct assessed by self-report questionnaires. Studies have shown that the general subjective perception of impact of fatigue does not significantly associate with walking, but the motor/physical subdomain of self-report questionnaires is associated with walking endurance [10]. State fatigue has been defined as the transient sensations of weariness or lack of energy during or right after a given task, described as an activity based fatigue or fatigability. Fatigability therefore has a perceived (subjective, i.e., perceived exertion) and performance (objective) component [11,12]. The prevalence of walking-related fatigability is up to almost half of the more disabled pwMS [13]. Results regarding changes in spatiotemporal parameters

after a prolonged walk (i.e., 6MWT), which could explain the deceleration over time, are not consistent. Once reductions in walking speed along with changes in cadence, step length, step time and double support have been reported for moderate to severe pwMS [14], opposite results have suggested no changes for moderate pwMS after the 6MWT [15], and alterations in cadence and step time have only been significant for ambulatory assistance pwMS [16].

Although changes in gait pattern (i.e., due to disease progression and/or after a walking task) can impair walking capacity, pwMS have learned to maintain mobility by taking regular rest breaks [17] . However, during uninterrupted prolonged walking (e.g., 6MWT), mild pwMS usually start walking with a moderate pace and keep the pacing strategy in order to do not decelerate until the end of the test, and moderate and severe pwMS significantly decelerate over time [13]. In addition, pwMS walk longer distances and present diminished perceived exertion when performing intermittent 6-minutes walking (i.e., three bouts of 2-minutes walking) [17] and, in the daily living, pwMS perform 8-times more of uninterrupted 2-minutes walking with moderate speed compared to uninterrupted 6-minutes walking [18].

Currently, the literature does not provide data concerning to the impact of intermittent-walking on gait pattern and on fatigability of pwMS and their association with trait fatigue, why the present study aims to investigate: 1) the effects of an intermittent-walking protocol on spatiotemporal gait parameters (absolute- and walk reserve-values), walking-related fatigability and perceived exertion of pwMS and HC; 2) the manifestation of walking-related fatigability and comparisons among HC, fatigable and non-fatigable pwMS; 3) the association of changes in spatiotemporal gait parameters with performed and perceived fatigability (i.e., walking-related fatigability and perceived exertion), trait fatigue, cognition and disease step. In addition, (4) to verify the association between trait fatigue and fatigability (subjective and objective) over the walking protocol.

2. Methods

Thirty-four eligible persons diagnosed with relapse-remitting MS [19] were recruited from neurological clinics and MS community organizations. Exclusion criteria were: confirmed MS relapse in the month prior to testing; significant cardiac or respiratory disease; not able to walk for 2-minutes without stopping. Twenty-eight HC matched for age, sex and weight were recruited.

Participants determined their disability level with the Patient Determined Disease Step scale (PDDS-BR). The Modified Fatigue Impact Scale (MFIS) was used to evaluate trait fatigue. The oral version of the Symbol digit modalities test (SDMT) was administered as a measure of cognitive function.

The spatiotemporal gait parameters with the participants' preferred walking speed (PWS) were measured prior to the intermittent-walking protocol using a 4.88-meter electronic walkway - GaitRite (CIR Systems Inc., Haverton, Pennsylvania, USA). The complete intermittent-walking protocol was composed of six 2-minutes walks with a rest period of 30 seconds between bouts, adding up to a total of 12 minutes of walking. Participants were instructed to walk along a 10-meter corridor, turning 180 degrees, during uninterrupted 2-minutes. Participants were instructed to "walk as fast as possible, but safely". If necessary, the use of a walking aid was allowed. Before, during the rest periods and after the last 2-minute walk, the rate of perceived exertion (RPE) was measured using the 15 points Borg Scale and the spatiotemporal gait parameters were assessed with the participants walking with their maximal/fast walking speed (FWS) on the GaitRite. Walking reserve (WR) for the following spatiotemporal parameters: speed, cadence and step length were calculated as the difference between each trial of FWS (before, during and after the intermittent-walking protocol) and the PWS [WR = FWS (pre to 6th- 2MW) – PWS]. In order to investigate walking-related fatigability, the distance walk index (DWI) from the second to the sixth 2-minutes walks were calculated [13].

Statistical analysis

Adopting a cut-off of 10% of deceleration (i.e., DWI $\leq$ -10) [20] in the sixth 2-minute walk (DWI6-1), pwMS were allocated into two groups: MS Fatigable (^{MS} – F) and MS Non-Fatigable (^{MS} – NF).

Statistical analyses were performed using GraphPad Prism version 7.03 (GraphPad Software, California, USA). Distribution of data was visually checked by box-plots, q-q-plots, histograms, dot-plots and the Shapiro-Wilk normality test. All baseline data were analysed using the unpaired t-test to compare HC vs MS All (i.e., all pwMS). One-way ANOVA followed by Tukey's Multiple Comparison Test was used for comparisons among HC, MS-NF and MS-F groups. In addition, One-way ANOVA verified the effect of time for each group. Two-way ANOVA was used to analyse the effects of time and groups. Changes in percentage of the spatiotemporal parameters were calculated [Change (%) = (FWS pre – FWS post, 6th –

2MW) / FWS pre) *100]. Pearson's and Spearman's coefficient were used to verify associations between changes in spatiotemporal gait parameters and fatigability (i.e., walking-related fatigability and perceived exertion), trait fatigue, cognition and disease step. Spearman's coefficient was used to verify associations between trait fatigue and fatigability. Level of statistical significance was set at $p < 0.05$.

3. Results

As shown in table 1, no differences were found between groups regarding participant's characteristics. Clinical results revealed that cognitive function was significantly reduced in pwMS vs HC, with no difference between ^{MS}-F and ^{MS}-NF. Concerning to trait fatigue, MFIS total and MFIS physical were significantly higher for pwMS vs HC and no differences have been found between ^{MS}-F and ^{MS}-NF. PwMS walked significantly less vs HC, and lower distance was reached by ^{MS}-F compared to ^{MS}-NF.

Table 1. Participant characteristics of the total sample and clinical results.

	HC	MS_{All}	$^{MS-}$NF	$^{MS-}$F
n (females)	28 (22)	26 (23)	18 (17)	8 (6)
Age, y	40.3 (37:45)	43.5 (39:48)	47 (36:57)	42 (37:47)
Height, m	1.66 (1.62:1.70)	1.64 (1.61:1.68)	1.69 (1.59:1.78)	1.62 (1.58:1.66)
Weight, kg	67.7 (62:73.3)	67.9 (61.6:74.2)	77 (61:92.9)	63.8 (57.7:70)
PDDS	---	1.38 (0.73:2.03)	2 (0.26:3.73)	1.1 (0.45:1.76)
Time since diagnosis, yrs	---	8.1 (5.4:10.9)	11.3 (3.9:18.8)	6.7 (4.1:9.4)
SDMT, score	63.3 (58.1:68.5)	47.1 (42.9:51.3)*	44 (34.1:53.8)*	48.6 (43.7:53.4)*
$MFIS_{total}$	24.6 (19.3:29.8)	40 (32.2:47.8)*	40 (26.1:53.8)*	40 (29.6:50.5)*
$MFIS_{cognitive}$	12.3 (9.3:15.2)	17.5 (13.5:21.4)	16.1 (9.4:22.7)	18.1 (12.8:23.3)
$MFIS_{physical}$	10.5 (7.9:13.1)	18.6 (15.1:22.1)*	20.1 (13:27.2)*	18 (13.6:22.4)*
$MFIS_{psychosocial}$	2 (1.3:2.7)	3.8 (2.8:4.8)*	3.7 (1.9:5.5)*	3.8 (2.5:5.1)
Distance $_{Total\ -\ 12\ min}$, m	1156 (1102:1210)	864 (768:960)*	722 (484:959)*+	927 (833:1022)*
DWI, %	-0.99 (-3.3:1.3)	-6.1 (-10.5:-1.7)	-19.1 (-25.9:-12.4)*+	-0.37 (-3.3:2.5)

Legend: Results are presented as mean and 95% confidence interval (CI). MS_{All}, all persons with MS. $^{MS-}$NF, non- fatigable persons with MS. $^{MS-}$F, fatigable persons with MS. PDDS, patient determined disease steps. MFIS, modified fatigue impact scale. DWI, distance walked index. Statistical significance ($p \leq 0.05$) are denoted by *****: different from healthy controls (HC), **+**: different from $^{MS-}$NF.

Figure 1 shows that pwMS walked less *vs* HC in all the 2-minutes walks and $^{MS-}$F group walked significantly less from the 3rd - to the 6th - 2MW compared to the $^{MS-}$NF group. The absolute-values of RPE were significantly higher for ^{MS}-F from the 3rd - to the 6th - 2MW

compared to HC, and at the 6th - 2MW for MS-NF *vs* HC. One-Way ANOVA revealed a significant increment in RPE at the 5th - and 6th - 2MW by MS-F, and at the 6th - 2MW by MS-NF compared to the 1st – 2MW.

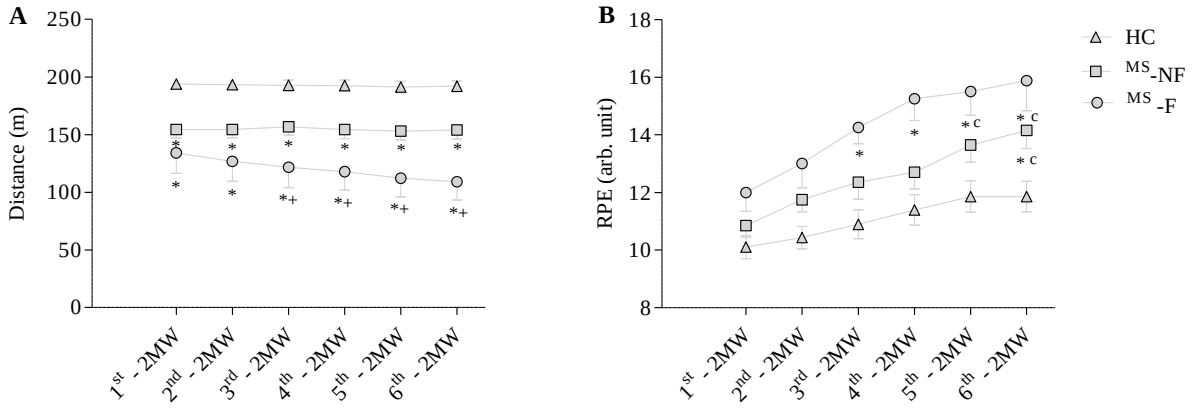

Figure 1. A, distance travelled in each 2-minute walk. B, rate of perceived exertion (RPE) in arbitrary units after each 2-minute walk. MS-NF, non- fatigable persons with MS. MS-F, fatigable persons with MS. Statistical significance ($p \leq 0.05$) are denoted by *****: different from healthy controls (HC), **+**: different from MS-NF, c: different from 1st – 2MW.

Table 2 presents the absolute-values of spatiotemporal parameters and comparisons between groups at baseline (pre) and over the intermittent-walking protocol. In general, pwMS walked significantly slower compared to HC. Concerning to walking speed, significant difference between MS-F and MS-NF was only found after the 5th – 2MW. Cadence did not show significant differences between groups, but step length was significantly shorter for pwMS *vs* HC and differences between MS-F and MS-NF were found after the 4th - and 5th - 2MW. Significant differences between pwMS *vs* HC could be found for swing (%GC), stance (%GC) and double support (%GC), but not for step time and base of support. Analysis over time revealed that only the MS-F group presented significant reduction in walking speed and step length from the 4th – to the 6th - 2MW, and in cadence after the 5th – and 6th - 2MW compared to the baseline values of FWS.

Table 2. Spatiotemporal gait parameters presented in mean (95% CI): comparisons between groups and time effect.

		PWS	FWS	1st - 2MW	2nd - 2MW	3rd - 2MW	4th - 2MW	5th - 2MW	6th - 2MW
Walking speed (m/s)	HC	1.24 (1.15:1.33)	1.90 **a** (1.80:2.0)	1.81 **a** (1.66:1.95)	1.78 **a** (1.64:1.91)	1.81 **a** (1.68:1.93)	1.86 **a** (1.77:1.95)	1.81 **a** (1.69:1.93)	1.83 **a** (1.71:1.94)
	MS_{All}	1.05 (0.96:1.14)	1.45*** a** (1.30:1.61)	1.44*** a** (1.30:1.58)	1.41*** a** (1.24:1.59)	1.44*** a** (1.28:1.60)	1.41*** a** (1.25:1.57)	1.36*** a** (1.20:1.51)	1.38*** a** (1.22:1.53)
	^{MS}-NF	1.06 (0.98:1.13)	1.45*** a** (1.28:1.62)	1.52 **a** (1.37:1.66)	1.48*** a** (1.30:1.66)	1.54 **a** (1.39:1.69)	1.51*** a** (1.35:1.66)	1.46 **a** (1.30:1.61)	1.48 **a** (1.32:1.64)
	^{MS}-F	1.04 (0.76:1.33)	1.45*** a** (1.05:1.86)	1.29*** a** (0.94:1.63)	1.27***** (0.79:1.75)	1.24***** (0.81:1.66)	1.21*** b** (0.79:1.63)	1.14***+ b** (0.75:1.52)	1.17*** b** (0.80:1.53)
Cadence (steps/min)	HC	108.4 (103:113)	136.9 **a** (131:143)	130.4 **a** (121:139)	128.4 **a** (121:136)	131.7 **a** (123:140)	134 **a** (129:139)	129.9 **a** (123:137)	130.6 **a** (125:137)
	MS_{All}	105.7 (100:111)	126.3 **a** (116:136)	126.9 **a** (120:134)	124 **a** (115:132)	125.4 **a** (117:134)	123.8 **a** (116:131)	121.2 **a** (113:129)	122.2 **a** (114:130)
	^{MS}-NF	105 (99:111)	123 **a** (110:135)	129.2 **a** (121:137)	123.9 **a** (115:133)	127.5 **a** (120:135)	125.6 **a** (117:134)	123.6 **a** (116:131)	124.7 **a** (116:133)
	^{MS}-F	105.6 (93:118)	130.1 **a** (112:149)	119.8 (104:136)	118 (92:144)	116.7 (93:141)	115.3 (95:136)	111.7 **b** (91:133)	112.9 **b** (93:132)
Step Length (cm)	HC	69.1 (66.4:71.9)	83.5 **a** (79.8:87.2)	82.9 **a** (79.4:86.5)	83.4 **a** (79.8:87.1)	82.8 **a** (78.9:86.6)	83.5 **a** (79.8:87.3)	83.2 **a** (79.3:87.1)	84 **a** (80:88)
	MS_{All}	59.9***** (56.3:63.4)	70.4***a** (66.3:74.5)	68.7***a** (64.7:72.8)	69.1***a** (64.6:73.6)	69.1***a** (65:73.3)	68.1***a** (63.4:72.8)	67.1***a** (62.4:71.8)	67.5***a** (63:71.9)
	^{MS}-NF	60.9 (57.7:64.1)	71.9***a** (67.8:76)	71.1***a** (67.2:75)	71.5***a** (67.3:75.6)	72.4***a** (68.9:75.9)	71.7***a** (67.7:75.7)	70.5***a** (65.9:75.2)	70.6***a** (66.1:75.1)
	^{MS}-F	57.7***** (47.1:68.3)	67.3***a** (56.3:78.3)	63.6***a** (53.2:74.1)	64.1***a** (51.9:76.3)	62.1***** (51.6:72.6)	60.5***+ b** (48.3:72.6)	59.9***+ b** (48.9:70.9)	60.8***b** (50.5:71.1)
Step Time (sec)	HC	0.54 (0.50:0.57)	0.49 **a** (0.37:0.61)	0.61 (0.35:0.86)	0.64 **a** (0.34:0.94)	0.68 **a** (0.30:1.07)	0.63 **a** (0.39:0.87)	0.57 **a** (0.37:0.76)	0.45 **a** (0.42:0.48)
	MS_{All}	0.55 (0.50:0.60)	0.68 (0.46:0.91)	0.73 (0.31:1.16)	0.52 (0.44:0.59)	0.47 (0.44:0.51)	0.50 (0.46:0.53)	0.49 (0.45:0.52)	0.52 (0.43:0.61)
	^{MS}-NF	0.57 (0.50:0.63)	0.79 (0.46:1.11)	0.77 (0.13:1.40)	0.48 (0.44:0.52)	0.48 (0.44:0.52)	0.48 (0.45:0.50)	0.48 (0.44:0.52)	0.51 (0.37:0.65)
	^{MS}-F	0.52 (0.43:0.61)	0.46 (0.40:0.52)	0.67 (0.29:1.04)	0.59 (0.34:0.84)	0.45 (0.37:0.53)	0.54 (0.44:0.63)	0.50 (0.43:0.58)	0.54 (0.44:0.63)
Base of Supp. (cm)	HC	9.59 (8.3:10.8)	8.9 (7.8:9.9)	8.91 (7.7:10)	9.24 (7.7:10.6)	8.86 (7.5:10.1)	8.96 (7.8:10)	8.50 (7.2:9.7)	9.31 (7.8:10.8)
	MS_{All}	10.26 (8.3:12.2)	8.98 (7.3:10.6)	10.33 (8.7:11.9)	11.16 (9.3:12.9)	10.07 (8.4:11.7)	10.31 (8.4:12.1)	10.41 (8.6:12.2)	9.41 (7.7:11)
	^{MS}-NF	9.33 (7.3:11.2)	8.28 (6.3:10.2)	9.87 (8:11.7)	10.6 (8.4:12.8)	9.28 (7.2:11.2)	9.71 (7.4:11.9)	9.81 (7.5:12)	8.96 (7:10.8)
	^{MS}-F	12.22 (7.1:17.3)	10.45 (7:13.8)	11.29 (7.4:15)	12.24 (8.5:15.9)	11.73 (8.3:15)	11.58 (7.3:15.7)	11.69 (8.1:15.2)	10.37 (6.3:14.3)
Swing (%GC)	HC	34.9 (32.2:37.5)	39 **a** (36.4:41.5)	38.6 **a** (36.8:40.5)	36.7 **a** (32.7:40.6)	35.1 **a** (30.9:39.4)	36.7 **a** (32.8:40.6)	36.2 (32.6:39.8)	37.1 (34.8:39.4)
	MS_{All}	31.8 (29.3:34.2)	36.1 **a** (33.7:38.5)	30.8***** (25.6:35.9)	34.2 **a** (30.8:37.5)	35 **a** (32.2:37.8)	36.1 **a** (34.2:37.9)	32.1 (28.1:36.2)	30***** (24.6:35.4)
	^{MS}-NF	33 (30.8:35.2)	36 **a** (32.5:39.4)	33.7 (28.5:39)	35.8 **a** (32.9:38.8)	37.7 **a** (36.2:39.3)	36.6 **a** (34.1:39.1)	32 (26.3:37.8)	28.9***** (21.1:36.6)
	^{MS}-F	29.2 (22.3:36.1)	36.4 **a** (33.4:39.5)	24.4*** b** (11.7:37.1)	30.6 (21.2:40)	29.2 (21.6:36.8)	35 (31.6:38.3)	32.4 (26.8:38)	32.4 (25.6:39.1)
Stance (%GC)	HC	65 (62.4:67.7)	61 **a** (58.4:63.5)	61.3 **a** (59.5:63.1)	63.3 **a** (59.3:67.2)	64.8 **a** (60.6:69)	63.2 **a** (59.3:67.1)	63.7 (60.1:67.3)	62.8 (60.5:65.1)
	MS_{All}	68.1 (65.7:70.6)	63.8 **a** (61.4:66.2)	69.2***** (64:74.3)	65.8 **a** (62.4:69.1)	64.9 **a** (62.1:67.8)	63.8 **a** (62:65.7)	67.8 (63.7:71.8)	69.9***** (64.5:75.3)
	^{MS}-NF	66.9 (64.7:69.1)	64 **a** (60.5:67.4)	66.2 (60.9:71.5)	64.1 **a** (61.1:67)	62.2 **a** (60.7:63.7)	63.3 **a** (60.8:65.8)	67.9 (62.1:73.7)	71.1***** (63.4:78.8)
	^{MS}-F	70.7 (63.7:77.6)	63.5 **a** (60.4:66.6)	75.5*** b** (62.9:88.2)	69.3 (60:78.7)	70.8 (63.2:78.3)	65 (61.6:68.3)	67.6 (62:73.2)	67.6 (60.8:74.3)
Double Supp. (%GC)	HC	32.5 (25.1:39.9)	19.2 **a** (16.3:22.1)	24 **a** (18.3:29.6)	21.3 **a** (16.8:25.9)	24.6 (17.4:31.7)	24 **a** (19.6:28.3)	21.1 **a** (16.7:25.4)	23 **a** (17.6:28.3)
	MS_{All}	37.5 (31.6:43.4)	27.7 **a** (24.1:31.3)	37***** (28.1:45.8)	26.4 **a** (23.2:29.6)	32 (26.6:37.5)	27.6 **a** (23.4:31.8)	30.8 **a** (24.6:37)	39.5***** (30.1:48.9)

$^{MS-}$NF	36.5 (29:44)	28.5 (24:33)	35.7***** (25.1:46.2)	24.6 **a** (22:27.1)	30.4 (24.1:36.7)	26.8 (21.6:32.1)	29.1 (21.3:36.9)	42.2***** (29.6:54.8)
$^{MS-}$F	39.2 (29.9:48.4)	25.3 **a** (20.1:30.4)	49.5*** b** (28.9:70.1)	35.2 (21:49.3)	37.8 (25.4:50.3)	29.9 (23.4:36.4)	34.5 (25.3:43.8)	34.1 (23:45.2)

Legend: PWS, preferred walk speed. FWS, fast walk speed. 2MW, 2-minutes walks. HC, healthy controls. MS_{All}, all persons with MS. $^{MS-}$NF, not-fatigable persons with MS. $^{MS-}$F, fatigable persons with MS. ***** denotes statistical significance ($p<0.05$) compared to HC. **+** denotes statistical significance compared to $^{MS-}$NF. **a** denotes statistical significance compared to PWS. **b** denotes statistical significance compared to FWS.

For pwMS, changes in percentage (i.e., after the intermittent-walking protocol) in spatiotemporal gait parameters were as follow [mean (95% CI)] for walking speed [-1.2 (-16:13) %], cadence [1.6 (-14:17) %], step length [-0.59 (-4:3) %], and for WR speed [-23 (-57:10) %], WR cadence [-53 (-143:36) %], WR step length [-0.56 (-29:28) %].

As shown in figure 2, $^{MS-}$F group showed significant differences *vs* HC and *vs* $^{MS-}$NF group regarding to WR speed and WR step length. In addition, for the $^{MS-}$F group, decrement in WR speed was already significant from the 2nd - 2MW to the 6th – 2MW, and for WR cadence and WR step length from the 3th – 2MW until after the 6th – 2MW compared to baseline-values of WR in the FWS.

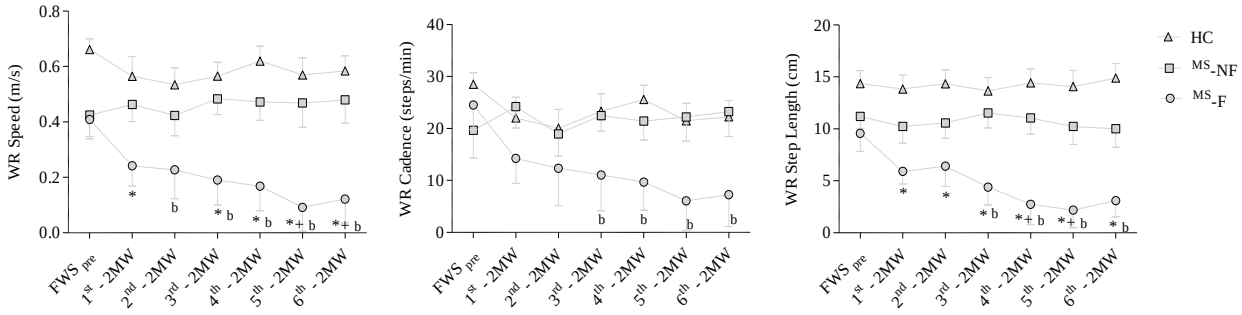

Figure 2. Walking reserve (WR) speed, cadence and step length over the intermittent-walking protocol. FWS, fast walk speed. 2MW, 2-minute walk. HC, healthy controls. $^{MS-}$NF, not-fatigable persons with MS. $^{MS-}$F, fatigable persons with MS. Results are presented as mean and standard error of mean. ***** denotes statistical significance ($p<0.05$) compared to HC. **+** denotes statistical significance compared to $^{MS-}$NF. **b** denotes statistical significance compared to FWS $_{pre}$.

Table 3 shows that the baseline-values of spatiotemporal gait parameters measured during the FWS were mostly associated with total distance travelled, perceived fatigability (i.e., RPE), trait fatigue, cognitive function and disease step, but not with performance fatigability

(DWI $_{6-1}$). On the other hand, the effects of the intermittent-walking protocol revealed that changes in walking and in WR speed and cadence were significantly associated with total distance, performance and perceived fatigability, cognitive function and disease step, but not with trait of fatigue.

Table 3. Coefficients of correlation R (p-value) between spatiotemporal gait parameters and total distance, performance and perceived fatigability, trait fatigue, cognitive function and disease step in persons with multiple sclerosis.

Spatiotemporal parameters	Distance $_{Total}$	DWI $_{6-1}$	RPE $_{6th-2MW}$	MFIS $_{Total}$	MFIS $_{Physical}$	SDMT	PDDS
Baseline FWS							
Speed	**0.77 (0.000)**	0.07 (0.7)	**-0.64 (0.000)**	**-0.54 (0.005)**	**-0.56 (0.003)**	**0.51 (0.009)**	**-0.67 (0.000)**
Cadence	**0.55 (0.004)**	-0.01 (0.9)	*-0.34 (0.08)*	**-0.41 (0.03)**	*-0.39 (0.05)*	0.22 (0.2)	**-0.56 (0.003)**
Step Length	**0.77 (0.000)**	-0.001 (0.9)	**-0.57 (0.002)**	**-0.62 (0.000)**	**-0.59 (0.001)**	**0.50 (0.009)**	**-0.53 (0.006)**
WR Speed	**0.63 (0.000)**	0.11 (0.5)	**-0.54 (0.004)**	**-0.65 (0.000)**	**-0.69 (0.000)**	**0.45 (0.02)**	**-0.56 (0.003)**
WR Cadence	*0.27 (0.1)*	-0.009 (0.9)	-0.20 (0.3)	**-0.46 (0.02)**	**-0.49 (0.01)**	0.11 (0.5)	*-0.32 (0.1)*
WR Step Length	**0.56 (0.00)**	*0.31 (0.1)*	**-0.49 (0.01)**	**-0.46 (0.01)**	**-0.45 (0.02)**	0.26 (0.19)	*-0.37 (0.06)*
Change (%)							
Speed	**0.53 (0.00)**	**0.65 (0.00)**	**-0.40 (0.04)**	-0.03 (0.8)	-0.12 (0.5)	*0.35 (0.08)*	**-0.45 (0.02)**
Cadence	**0.54 (0.00)**	**0.57 (0.00)**	**-0.50 (0.009)**	-0.10 (0.6)	-0.18 (0.3)	**0.42 (0.03)**	*-0.38 (0.05)*
Step Length	-0.006 (0.9)	*0.33 (0.09)*	0.18 (0.38)	*0.27 (0.1)*	0.16 (0.4)	0.08 (0.6)	-0.09 (0.6)
WR Speed	**0.64 (0.000)**	**0.65 (0.000)**	**-0.48 (0.01)**	-0.02 (0.9)	-0.18 (0.2)	0.24 (0.2)	**-0.68 (0.000)**
WR Cadence	**0.67 (0.000)**	**0.50 (0.01)**	**-0.55 (0.003)**	-0.14 (0.5)	-0.23 (0.2)	-0.07 (0.7)	**-0.66 (0.000)**
WR Step Length	-0.18 (0.3)	0.01 (0.9)	0.22 (0.2)	0.22 (0.2)	0.13 (0.5)	*0.23 (0.05)*	0.25 (0.2)

Legend: DWI, distance walked index; RPE, rate of perceived exertion; MFIS, modified fatigue impact scale; SDMT, symbol digit modality test (oral version); PDDS, patient determined disease steps. Statistical significances ($p \leq 0.05$) are highlighted with bold letters. Italic letters denote trend to statistical significance ($p \leq 0.10$).

Concerning the associations between trait fatigue and fatigability over the intermittent-walking protocol, see table 4. The results revealed no association between trait fatigue and performance fatigability, but significant associations were found between trait fatigue and perceived fatigability all over the walking protocol.

Table 4. Spearman coefficient of correlation R (p-value) between trait fatigue and fatigability in persons with multiple sclerosis.

	State Fatigue										
Trait Fatigue	DWI_{2-1}	DWI_{3-1}	DWI_{4-1}	DWI_{5-1}	DWI_{6-1}	RPE 1st – 2MW	RPE 2sd – 2MW	RPE 3th – 2MW	RPE 4th – 2MW	RPE 5th – 2MW	RPE 6th – 2MW
MFIS $_{total}$	-0.05 (0.7)	0.08 (0.7)	0.01 (0.9)	0.05 (0.8)	0.08 (0.6)	**0.55 (0.003)**	*0.33 (0.1)*	**0.49 (0.01)**	**0.40 (0.04)**	**0.54 (0.005)**	**0.54 (0.004)**
MFIS $_{physical}$	-0.11 (0.5)	-0.01 (0.9)	-0.07 (0.7)	-0.05 (0.7)	-0.02 (0.9)	**0.66 (0.000)**	**0.44 (0.02)**	**0.53 (0.006)**	**0.46 (0.01)**	**0.56 (0.003)**	**0.55 (0.003)**

Legend: DWI, distance walked index; RPE, rate of perceived exertion; MFIS, modified fatigue impact scale; Statistical significances ($p \leq 0.05$) are highlighted with bold letters. Italic letters denote trend to statistical significance ($p \leq 0.10$).

4. Discussion

The main findings of the present study were that changes in spatiotemporal gait parameters and the manifestation of perceived and performance fatigability could be found in pwMS over the intermittent-walking protocol. However, the slowdown in walking speed, reductions in absolute-values of cadence and step length, as well as the increment in perceived exertion were dependent on the manifestation of performance fatigability (i.e., for pwMS presenting walking-related fatigability).

In general, pwMS travelled shorter distances, walked slower and presented shorter step length compared to HC, but no differences could be found among HC, ^{MS} – NF and ^{MS} – F for absolute-values of cadence. Comparisons of baseline-values have shown that no differences in spatiotemporal gait parameters, except for step length, could be found between pwMS *vs* HC for the PWS, but walking speed and step length were significantly impaired in pwMS compared to HC during FWS $_{pre}$. The results are in line with findings from the literature, were differences between HC and pwMS seems to appear as the walking speed for short walk tests increases [21]. Interestingly, WR speed, WR cadence and WR step length were not significant different between groups during FWS, revealing that pwMS and HC presented similar ability of increasing speed, cadence and step length in response to a different environmental demand (i.e., from preferred to maximal walk speed). From our knowledge, there is no studies comparing WR between pwMS and HC. However, with mean-value of about 0.42 of WR speed from our sample, our result corroborate with findings from Kalron et al. [8] for low disable pwMS, who found a mean-value of 0.47 m/s in WR speed.

Regarding to the effects of the intermittent-walking protocol, our results suggest that changes in spatiotemporal gait parameters could only be found in those pwMS who decreased walking performance over time. When analysing the results from all pwMS in the same group, no effects of the intermittent-walking protocol could be found, which is in agreement with previous studies for low to moderate disable pwMS after the 6MWT [14,15,22]. However, analysis of subgroups revealed that ^{MS} – F group started to deteriorate absolute-value of walking speed and step length after the 4^{th} – 2MW and cadence after the 5^{th} – 2MW, even when the walking-protocol allowed short rest breaks. This results highlight the importance of identifying

a specific group of pwMS that shows decline in walking performance and reduce walking speed, cadence and step length in order to deal with fatigue, presenting a more conservative strategy as has also been found in young adults after fatiguing tasks [23]. In addition, WR speed and WR step length revealed to be a very interesting marker of decrement in performance and, consequently, of alterations in spatiotemporal parameters. Already from the beginning of the protocol, ^{MS} – F group reduced their WR presenting significant differences from HC and later on from ^{MS} – NF group, as well as, the decline in WR continued and started to be significantly different from FWS $_{pre}$ at the 2^{nd} – 2MW for speed and at 3^{rd} – 2MW for cadence and step length. Thus, the ability of altering gait pattern decreases as motor fatigue is installed and it may reduce walking speed during activities of daily living. In addition, reduced walking speed is accompanied by loss of community ambulation and increase in the energetic cost of walking [24].

Concerning the perceived fatigability, values of RPE were significantly higher for ^{MS} – F persons compared to HC from the 3^{rd} – 2MW to the 6^{th} – 2MW, as well as, increased significantly compared to the 1^{st} – 2MW from the 5^{th} – 2MW. ^{MS} – NF group also increased the RPE-value after the last bout of 2MW, although this not came along with alterations in spatiotemporal gait parameters. It seems that perceived fatigability is also involved on the modulation of gait pattern during prolonged walking for pwMS, and a portion of this population starts to perceive fatigability and also alter gait pattern before others. There are no comprehensive studies on the investigation of walking-related fatigability determinants, however, one study from our group [25] have found that knee flexor strength and balance control may explain decline in walking during the 6MWT.

The associations of gait parameters from the baseline-values (FWS $_{pre}$) showed statistical significance with total distance travelled, perceived fatigability, trait fatigue, cognitive function and disease step for pwMS. However, no associations were found with performance fatigability (i.e., DWI), which is also explained by the non-significant differences in baseline-values of gait parameters between ^{MS} – F and ^{MS} – NF groups. The results suggest that the manifestation of walking-related fatigability did not depend on the level of gait pattern dysfunction and possible occur in a random manner for pwMS. There are potential avenues for new studies aiming to investigate determinants of walking-related fatigability, and why some of the MS patients decline performance over time during exercise and others do not. Unfortunately, we could not find studies investigating the relation of short walking capacity (e.g., T25FW) speed with performance fatigability, and the only study we have found identified

that concentric fatigability (i.e., continuous dynamic contractions of the knee extension) significantly explained 9% and 16% of the variance in the 6MWT and in the MSWS-12 (multiple sclerosis walking scale), respectively. On the other hand, walking dysfunction or altered gait pattern was associated with perceived fatigability, trait fatigue, cognitive function and disease step, and these findings have been reported in the literature [26–28].

Concerning to changes in the spatiotemporal gait parameters as an effect of the intermittent-walking protocol, significant associations were found with total distance travelled, performance and perceived fatigability and disease step. Interestingly, changes occurred in cadence presented significant associations, while changes in step length did not, although changes in step length have been more emphasized for the ^{MS} – F group. This could be explained by the sample size of the ^{MS} – F group. In addition, changes in gait pattern have not been associated with trait fatigue, leading to the conclusion that decline in performance is not associated with the frequent, prolonged, or constant sensation of fatigue over longer time frames, and the same result has been shown by Drebinger et. al. [22]. Although studies have suggested that central muscle activation decreases in fatigued patients (i.e., using a score from fatigue scale), and the difference between fatigued and non-fatigued pwMS might increase as the exercise period increases [29], pwMS presenting walking-related fatigability did not present any difference regarding trait fatigue when compared do $^{MS-}$ NF group. However, associations between walking capacity and impaired central muscle activation measured by a twitch interpolation technique have been found in pwMS [30], and future studies are necessary to identify the role of central activation on performance fatigability in pwMS.

Trait fatigue and perceived fatigability have been significantly associated in our sample of pwMS, corroborating with previous study [22]. This finding suggest that trait fatigue could impact perceived exertion during exercise, however decline in performance might be more impacted by other symptoms such as muscle weakness, spasticity, balance impairment and energy cost of walking [25,28,30], as well as lower level of physical activity and sedentary behaviours.

Although this is the first study to investigate the effects of an intermittent-walking protocol in spatiotemporal gait parameters and the association with performance and perceived fatigability, trait fatigue, cognitive function and disease step, the study presents some limitations such as the small sample size in the ^{MS} – F group and the low to moderate level of dysfunction of pwMS. On the other side, the results highlight the importance of identifying

determinants of performance fatigability once it was not associated with walking dysfunction and trait fatigue. In addition, the use of a cut off to identify pwMS presenting walking-related fatigability is interesting in order to select only those pwMS presenting performance fatigability and to investigate factors associated with it. Practical applications include the suggestion of incorporating intermittent-walking in physical exercise and/or rehabilitation interventions for pwMS in order to train patients to walk in their maximal speed during a short period of time, although the period of rest and the number of walks could be defined according to the increment in perceived exertion. Furthermore, even pwMS presenting high trait fatigue could be beneficed of intermittent-walking training.

Conclusions

In general, pwMS travelled shorter distances, walked slower and presented shorter step length compared to HC. However, the effects of the intermittent-walking protocol with alterations in absolut-values and in walking reserve of walking speed, cadence and step length, as well as significant increment in perceived exertion were dependent on the manifestation of performance fatigability (i.e., for pwMS presenting walking-related fatigability). Walking dysfunction was associated with perceived fatigability, trait fatigue, cognitive function and disease step. Trait fatigue was associated perceived fatigability but not with performance fatigability.

Conflict of interest statement

CR, ARD, FG and ACD declares no conflict of interest.

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4. CONSIDERAÇÕES FINAIS

A presente tese de doutorado teve como objetivo principal quantificar déficits na capacidade de caminhar de pessoas com EM comparado à indivíduos saudáveis, sem o diagnóstico da doença, e identificar os determinantes motores e a contribuição destes para o desempenho no caminhar. Assim, os achados principais dos estudos que compõem este trabalho estão ilustrados na figura 4. Primeiramente, sobre a avaliação da capacidade de caminhar na EM, os principais testes sugeridos na literatura e também utilizados nos estudos supracitados foram o T25FW, 2MWT e o 6MWT, além dos testes de curta distância utilizando tapetes instrumentalizados como o sistema GaitRite e de caminhadas intermitentes. Em todos os estudos realizados para esta tese de doutorado foram encontrados déficits na capacidade de caminhar em pessoas com EM, sejam eles na velocidade de caminhar curtas distâncias, na distância percorrida em testes de média e longa duração ou na fadigabilidade motora relacionada ao caminhar, esta implicando na desaceleração significativa do caminhar de parte dos pacientes com EM. O déficit relativo na capacidade de caminhar foi de aproximadamente de 20% para as pessoas com EM, em geral, comparadas aos indivíduos controle saudáveis sem o diagnóstico da doença. No entanto, os déficits no caminhar variaram de acordo com o nível de incapacidade dos pacientes, com valores de aproximadamente 10% a 30% para pessoas com EM, sem e com a percepção de incapacidades no caminhar por meio da PDDS, respectivamente. Além disso, para pessoas com EM que apresentaram fadigabilidade motora relacionada ao caminhar, o déficit na capacidade de caminhar foi de aproximadamente 35% versus 15% apresentado pelos pacientes não fadigáveis. Curiosamente, a fadigabilidade motora relacionada ao caminhar se fez presente em parte da população diagnosticada com EM, mesmo que a maioria dos pacientes com EM inseridos nos estudos apresentassem grau leve a moderado da doença. A prevalência de pessoas com EM que apresentaram fadigabilidade motora relacionada ao caminhar foi em média de 35% considerando os estudos que investigaram o índice de desaceleração no caminhar.

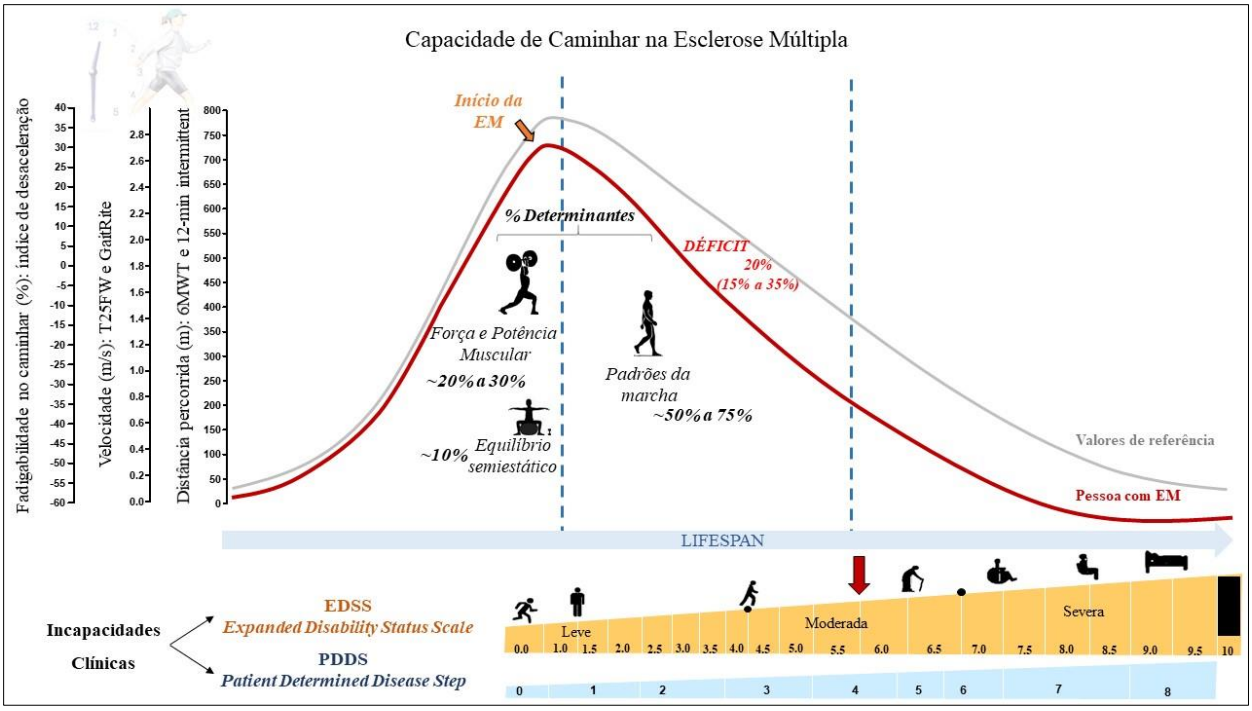

Figura 4. Ilustração dos resultados principais da pesquisa.

Com relação aos determinantes motores investigados e a contribuição destes para a capacidade de caminhar de pessoas com EM, a força muscular do membro inferior mais comprometido pela doença explica de 20% a 30% a variação na capacidade de caminhar curta e longa distâncias, independente do grupo muscular, tipo e velocidade de contração muscular. Especificamente, a força dos músculos flexores do joelho contribuiu com 27% para a desaceleração no caminhar durante o teste de caminhada prolongada (6MWT) em pessoas com EM e com grau leve de incapacidade da doença. Além disso, em um modelo que inseriu o equilíbrio semiestático e a força dos flexores do joelho, estes determinantes motores explicaram 39% da variação do caminhar de pessoas com EM.

Interessantemente, os déficits encontrados na potência muscular durante os testes de flexão plantar e de sentar e levantar na plataforma de força foram maiores comparados aos déficits encontrados na força. Além disso, tanto a potência quanto a força muscular foram associadas à capacidade de caminhar com valores de variaram de 15% a 33% para explicar a variação na velocidade de caminhada de curta distância. No entanto, a potência e força dos músculos envolvidos nos movimentos de flexão plantar e de sentar e levantar não foram associados com a fadigabilidade motora relacionada ao caminhar. Já a fadigabilidade motora relacionada ao caminhar durante o protocolo intermitente de 12 minutos de caminhada (6 x 2-

min), foi acompanhada de reduções na potência e força musculares e de alterações na velocidade do caminhar em pessoas com EM.

Considerando as alterações nos padrões da marcha, por meio da análise dos parâmetros espaço-temporais, as variáveis de velocidade e comprimento do passo apresentaram déficit significativo para pessoas com EM quando comparadas à indivíduos saudáveis, independentemente da presença de fadigabilidade motora. No entanto, os efeitos do protocolo intermitente de caminhada nas variáveis espaço-temporias foram somente significativos para as pessoas com EM que apresentaram fadigabilidade motora relacionada ao caminhar. E a capacidade de reserva da marcha para a velocidade, cadência e comprimento do passo dimiuiram significativamente ao longo do protocolo intermitente caminhada para pessoas fadigáveis e diagnosticadas com EM. Além disso, as mudanças relativas nas variáveis espaço-temporais da marcham explicam de 50% a 67% da variação na distância total percorrida em 12 minutos intermitentes de caminhada e da fadigabilidade motora relacionada ao caminhar.

4.1 Limitações dos estudos

Embora a presente tese de doutorado apresente estudos originais com a quantificação de déficits na capacidade de caminhar, investigado por meio de diferentes protocolos de caminhada, assim como déficit na força e potência muscular de membros inferiores, avaliados durante contrações isocinéticas e dinâmicas por meio de testes funcionais, algumas limitações podem ser elencadas: (1) parte dos estudos foram de caráter transversal dificultando a compreensão causa-efeitos dos determinantes motores na capacidade de caminhar de pessoas com EM; (2) a maioria dos pacientes diagnosticados com EM apresentavam grau leve a moderado da doença, não tendo representatividade nesta tese os pacientes com grau severo de incapacidade; (3) os pacientes com EM incluídos nos estudos apresentavam idade entre 18 e 60 anos. Assim, os déficits na capacidade de caminhar de adolescentes e idosos diagnosticados EM não foram quantificados e inseridos no modelo da figura 4; (4) somente as pessoas diagnisticadas com a forma remitente-recorrente da EM foram inseridas nos estudos experimentais. Desta forma, os estudos não investigaram déficits motores em pacientes com EMSP e EMPP.

4.2 Conclusões

Pessoas diagnosticadas com EM, com grau leve a moderado de incapacidade, apresentaram déficits na capacidade de caminhar que variaram de 15% a 35% dependendo do estado de incapacidade da doença quando comparados à indivíduos saudáveis sem o diagnóstico

de EM. Aproximadamente 35% dos indivíduos com EM inseridos na amostra desta tese manifestaram fadigabilidade motora relacionada ao caminhar, com mais de 10% de desaceleração durante o caminhar de média e longa duração.

O comprometimento dos determinantes motores de força e potência dos músculos dos membros inferios, equilíbrio semiestático e alterações nos padrões da marcha, contribuíram de forma significativa para a diminuição na capacidade de caminhar de pessoas com EM.

Contudo, uma vez que os determinantes motores supracitados são fatores modificáveis, principalmente pela prática de exercícios físicos, pessoas com EM devem inserir o exercício físico como parte do tratamento em conjunto com as terapias convencionais. Assim, mesmo que o paciente não reporte alterações na capacidade de caminhar ou apresente grau leve da doença, a prática de exercícios físicos se faz necessária a fim de gerar adaptações musculares, no equilíbrio postural e no controle motor da marcha, auxiliando no tratamento dos sintomas e na prevenção da incapacidade de caminhar.

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6. ANEXOS

6.1 Artigos publicados e artigos aceitos para publicação

Annals of Physical and Rehabilitation Medicine 63 (2020) 123–137

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Review

The importance of lower-extremity muscle strength for lower-limb functional capacity in multiple sclerosis: Systematic review

Cintia Ramari [a,*], Lars G. Hvid [b], Ana Cristina de David [a], Ulrik Dalgas [b]

[a] Faculty of Physical Education, University of Brasilia, Brasília, Brazil
[b] Section for Sport Science, Department of Public Health, Aarhus University, Aarhus, Denmark

ARTICLE INFO

Article history:
Received 14 June 2019
Accepted 11 November 2019

Keywords:
Multiple sclerosis
Lower-extremity
Muscle mechanical function
Functional capacity
Walking capacity

ABSTRACT

Background: Lower-limb functional capacity is impaired in most people with multiple sclerosis (PwMS). Reductions in lower-extremity muscle mechanical function (e.g., muscle strength) appear to have critical implications for lower-limb functional capacity. However, no review has summarized the current knowledge about the importance of muscle strength for functional tasks in PwMS. Expanding the current knowledge would advance the design of both clinical and research interventions aiming to improve functional capacity in PwMS.
Objectives: (1) To identify studies that measured lower-extremity muscle mechanical function and lower-limb functional capacity outcomes in PwMS, and (2) to map associations between muscle strength and functional capacity.
Methods: This review was based on a literature search (databases: PubMed, Embase). Included studies had to report data on lower-extremity muscle mechanical function and lower-limb functional capacity outcomes in PwMS. The associations between muscle strength and functional capacity were analyzed by using the reported correlation coefficients (R) recalculated to the determination coefficient R^2. Randomized trials and observational studies were included.
Results: A total of 59 articles were reviewed; 17 (773 participants) reported associations between muscle strength and functional capacity. Lower-extremity muscle mechanical function explained a significant part of the variance in most lower-limb functional capacity tests (approximately 20–30%). This was particularly evident in muscle strength from the weakest leg. Muscle strength was predominantly tested on knee extensors and knee flexors by using isokinetic dynamometry during maximal isometric (0°/s) and dynamic (30–60°/s) contractions. Walking tests such as the timed 25-Foot Walk Test and 10-Min, 2-Min and 6-Min Walk Test were the most frequently performed functional capacity tests.
Conclusions: In PwMS, muscle strength of particularly the weakest limb explains 20% to 30% of the variance across a number of lower-limb functional capacity tests. Thus, exercise programs should focus on increasing lower-extremity muscle mechanical function in PwMS and minimizing strength asymmetry between limbs.

1. Introduction

Lower-limb functional capacity is impaired in most people with multiple sclerosis (PwMS), as exemplified by the high prevalence of walking impairments in MS, with up to 68% of individuals experiencing some degree of ambulatory dysfunction [1,2]. Moreover, PwMS with both an early and long-term diagnosis perceive walking as their most important bodily function [3,4]. Such findings emphasize the importance of maintaining lower-limb functional capacity at the highest possible level in PwMS. As such, it seems essential to identify modifiable determinants of lower-limb functional capacity and then develop interventions targeting these.

Among several identified determinants of lower-limb functional capacity, including balance and cardiorespiratory capacity [5,6], muscular strength clearly stands out. Reductions in muscle mechanical function, comprising isometric strength, dynamic

* Corresponding author. Faculty of Physical Education, University of Brasília, Campus Universitário Darcy Ribeiro – Asa Norte – Brasília-DF, Faculdade de Educação Física, 70910-970 Brasília, Brazil.
E-mail addresses: cintiaramari@yahoo.com.br, cintiaramarif@gmail.com (C. Ramari), lhvid@ph.au.dk (L.G. Hvid), acdavid@unb.br (A.C.d. David), dalgas@ph.au.dk (U. Dalgas).

https://doi.org/10.1016/j.rehab.2019.11.005
1877-0657/

strength, "explosive" strength (rapid force development [RFD]), and power [7], appear to have critical implications in PwMS [8] on all levels of the International Classification of Functioning, Disability and Health model including activity level [9]. The lower-extremity is of particular importance because in MS, much larger muscle strength deficits are seen in the lower than upper extremity [8]. Some studies show that reduced lower-extremity muscle strength of particularly the weaker leg [10] negatively affects walking performance [10–13], balance [12,14,15], stair climbing and sit-to stand ability [10,13,16,17]. This is likely related to the lower physical activity levels often observed in PwMS as compared with healthy controls [17]. Because reduced muscle strength is associated with increased risk of all-cause mortality [18], cardiovascular disease, metabolic syndrome, osteoporosis and some forms of cancer in the general population [19–21], such health-related risks are likely also increased in PwMS. However, reviews evaluating the association of muscle strength in lower-extremity muscle groups with lower-limb functional capacity are lacking in PwMS. Such knowledge would advance our general understanding of the importance of lower-extremity muscle strength in PwMS and potentially also help guide the design of effective exercise interventions aimed at improving lower-limb functional capacity in PwMS.

Hence, to expand our understanding of the importance of muscle strength for functional capacity in PwMS, we performed a systematic literature review to:

- identify studies that measured lower-extremity muscle mechanical function and lower-limb functional capacity in PwMS;
- map existing associations between lower-extremity muscle mechanical function and lower-limb functional capacity in PwMS to allow for extracting relevant association patterns.

2. Methods

2.1. Study selection

The present review focused on English-language studies examining lower-extremity muscle mechanical function and lower-limb functional capacity in PwMS. The review was based on a literature search of 2 databases (PubMed, Embase) to retrieve cross-sectional and intervention studies published before February 2019. Review articles were not included. An independent search methodology aiming to identify relevant studies reporting data on muscle strength and functional tasks in MS was applied. The MeSH search terms included "Muscle Strength" AND ["Exercise Test" OR "Walk Test"] AND "Multiple Sclerosis". Single-case and case reports ($n < 5$) were excluded. Studies with no methodological description of the relevant measurements, that applied subjective muscle strength evaluations (e.g., scales), and with no data on muscle strength or functional tasks were also excluded.

2.2. Muscle mechanical function and functional capacity outcomes

Muscle mechanical function outcomes from the identified studies were reviewed, and data extraction included data on the involved lower-extremity muscle group(s), the type and velocity of the muscle contraction(s), and whether it was the strongest or weakest lower-limb (or most/least affected) that was used when performing the strength test(s). In addition, the type of device(s) used to assess muscle strength and the unit(s) used to report muscle strength were recorded.

Concerning functional capacity involving the lower limbs, the outcomes were reviewed according to the tests performed to evaluate mobility, balance, lower-limb strength, and short walking capacity (e.g., the timed 25-Foot Walk Test [T25FWT]) and long walking capacity (e.g., the 6-Min Walk Test [6MWT]). Also, data describing a potential association between lower-extremity muscle mechanical function and lower-limb functional capacity were extracted. Additional tests that were reported in the studies and related to the lower-limb capacity were reviewed, including those based on subjective scales.

2.3. Data analysis

The recorded associations between lower-extremity muscle mechanical function and lower-limb functional capacity were analysed using the reported correlation coefficients (R). The R coefficients were squared if not already done and reported as R^2 values. To map the associations, when the study performed more than one evaluation using the same method to assess muscle mechanical function, mean and 95% confidence intervals (CIs) of R^2 values were calculated. The included studies reported different sample sizes and sex ratio, which could be considered confounding factors when evaluating the association between strength and functional outcomes. Therefore, when determining the overall pattern across existing studies on the association for each lower-extremity muscle group, mean and 95% CIs of R^2 values were weighted by sample size and sex ratio (women/men) from each study. Because most of the studies evaluated knee extensor and flexor muscle strength, we could use these outcomes to report the R^2 values according to the type of contraction (isometric or dynamic). All data analyses were conducted with SPSS 25.0 (SPSS Inc.).

3. Results

3.1. Study selection

The selection of studies is in Fig. 1. We found 123 and 98 articles in PubMed and EMBASE, respectively. After removing 32 duplicates, 189 articles were screened by the abstracts and 99 articles were excluded. Finally, 59 articles were included in the review and are depicted in Table 1 along with the methods applied for assessment of lower-extremity muscle mechanical function and lower-limb functional capacity.

Most studies had a sample size of 20 to 60 participants regardless of study type (cross-sectional or intervention), although the articles from Callesen et al. [14] and Thoumie et al. [12] had sample sizes of 90 and 100 participants, respectively. The mean age was 30 to 50 years, with a higher prevalence of women. Most studies reported expanded disability status scale (EDSS) scores to classify the level of disability (general inclusion criteria ≤ 6.5), with the range of mean values of 2.8 to 6.5. Regarding lower-extremity muscle mechanical function, the most commonly used device was the isokinetic dynamometer followed by the handheld dynamometer. The muscle mechanical function of several muscle groups was evaluated with the knee extensor and flexor muscles most frequently. Lower-limb functional capacity tests were applied, predominantly focused on walking ability, with the T25FWT and the 6MWT the most frequent choices when evaluating short and long walking distance, respectively. Furthermore, a large number of studies evaluated gait parameters including velocity by an instrumented walkway or other gait analysis devices [6,12,13,22–26]. To evaluate mobility and dynamic balance, the Timed Up and Go test (TUG) was the most-used test, whereas the Sit-to-Stand test was the most-used test to provide a proxy measure of lower-extremity muscle strength. To evaluate balance alone, the most-used functional test was the Berg Balance Scale.

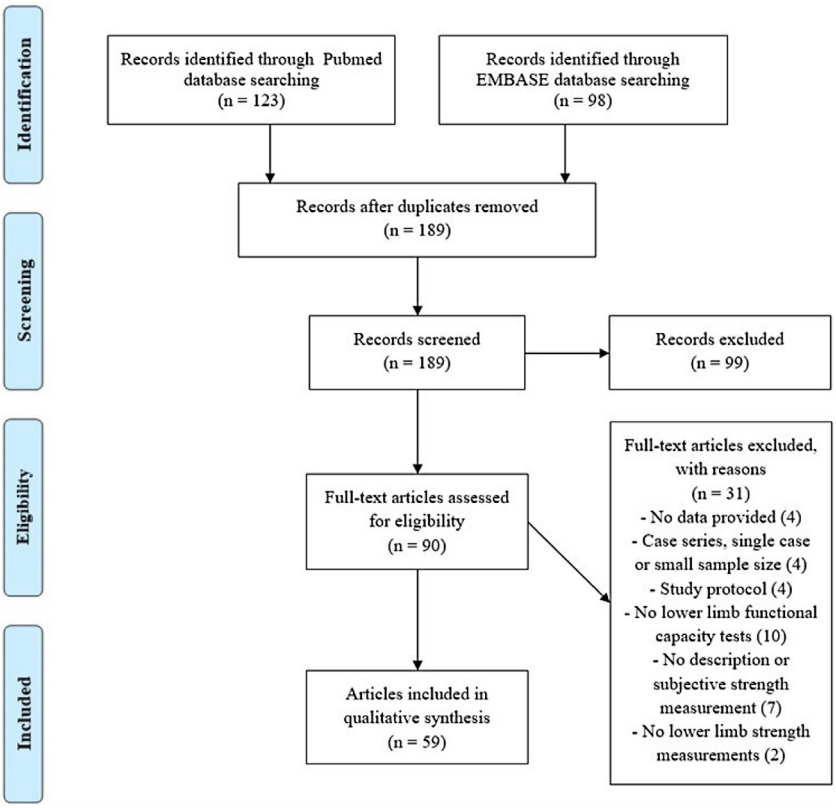

Fig. 1. Flowchart of search results and study selection for the review.

Table 2 summarises data from 17 articles reporting on the association between lower-extremity muscle mechanical function and the most frequently performed lower-limb functional capacity tests. Because most studies provided results on maximal isometric or dynamic muscle strength but only few on "explosive" muscle strength (RFD), associations with the latter outcome were excluded from the overall analysis. Most studies focused on the knee extensor and/or the knee flexor muscles, but studies from Almuklass et al. [27], Callesen et al. [14], Ng et al. [28] and Wagner et al. [29] also evaluated muscle strength of plantar flexor and/or dorsal flexor muscles; the study from Møller et al. [30] evaluated muscle strength of the hip extensor and hip flexor muscles. Mañago et al. [15] performed the most comprehensive evaluation of the association between lower-extremity muscle strength and lower-limb functional capacity: in addition to knee flexion and extension, this study also included hip extension, flexion, abduction, and adduction and ankle plantar flexion as well as trunk flexion. A large number of studies examined both the weakest (≈ most affected) and the strongest (≈ least affected) leg. Finally, most studies reported isometric muscle strength and/or slow dynamic muscle strength (30–60°/s).

3.2. Associations between lower-extremity muscle mechanical function and lower-limb functional capacity across muscle groups and limbs

Fig. 2 presents the association between muscle strength of different muscle groups of the weakest and strongest limb and specific measures of lower-limb functional capacity. The most frequently investigated muscle groups were the knee extensors and flexors, which were related to short and long walking performance (R^2 range = 0.18–0.34), TUG (R^2 range = 0.14–0.20) and sit-to-stand (R^2 range = 0.07–0.34) (significant according to mean R^2 and 95% CIs). The overall pattern showed comparable relationships between the knee flexors and extensors and functional capacity outcomes assessing short and long walking, and TUG and sit-to-stand (R^2 range = 0.11–0.34 vs 0.07–0.34) (significant according to mean R^2 and 95% CIs). In addition, we found a general pattern showing slightly stronger associations with the different lower-limb functional capacity outcomes for the weakest leg as compared with the strongest leg (R^2 range = 0.11–0.42 vs 0.00–0.34). Furthermore, the Sit-to-Stand test seemed to be the most sensitive outcome for identifying muscle strength asymmetry between the weakest and strongest limbs (R^2 range = 0.24–0.42 vs 0.07–0.34).

3.3. Contraction types

Because data on isometric (0°/s) and dynamic (60°/s) muscle strength of both the knee extensors and flexors were frequently reported (Table 2), along with their association with walking capacity, these results were specifically selected and summarized in Table 3. Overall, muscle strength of both knee extensors and flexors showed comparable associations with short and long walking capacity outcomes when tested isometrically and dynamically (according to mean R^2 and 95% CIs; Table 3). The only exceptions were for the association between isokinetic knee extensor strength and long walk (2 studies only) and between knee flexor muscle strength and long walk (1 study only). Although based on limited data and thus not shown in Table 3, RFD for both the knee extensors and flexors appears to display similar associations with walking capacity as isometric and dynamic muscle strength (Table 2).

Table 1
Descriptions of articles evaluating lower-limb muscle strength and functional capacity.

Authors	Study characteristics			Muscle mechanical function		Functional capacity tests
	Study type Sample size (*n*, women/men) Age (years)	Time since diagnosis (years) EDSS/PDDS score Type of MS (RR, SP, PP)	Testing device	Contraction type Joint: movement Leg	Strength outcome	Lower-limb functional capacity outcomes
Almuklass et al. [27]	Cross-sectional *n* = 23 (14/9) 56.0 ± 7.3 years	NR PDDS: 3.5 ± 1.0 RR	Strain gauge transducer	Isometric Ankle: plantarflexion Dorsiflexion Both	MVIC, Nm	6MWT, m T25FWT, m MSWS-12
Almuklass et al. [38]	Intervention *n* = 27 (NR) 54.0 ± 9.0 years NR	NR PDDS: 3.0 ± 1.3 RR	Strain gauge transducer	Isometric Ankle: plantarflexion Dorsiflexion Both	MVIC, Nm	6MWT, m T25FWT, m MSWS-12
Bayraktar et al. [39]	Intervention Group 1: *n* = 11 (11/0) 38 (33–48) years Group 2: *n* = 7 (7/0) 39 (27–47) years	Group 1: 6 (2.75–10.5) years Group 2: 1.5 (0.4) years EDSS, Group 1: 1 (2) Group 2: 2 (12) NR	Handheld dynamometer	Isometric Hip: flexion, extension, adduction, abduction Knee: flexion, extension Ankle: dorsiflexion Dominant	MVIC, lb	One-leg standing balance, sTUG, s 6MWT, m
Beier et al. [46]	Intervention Group 1: *n* = 25 44.6 ± 10.87 years Group 2: *n* = 57 47.7 ± 9.87 years (66/16)	NR NR RR/PP/SP	Cybex isokinetic dynamometer	Isokinetic Knee: extension, flexion Both	MVDC, ft/lb	T25FWT, s
Bowser et al. [16]	Cross-sectional Group 1: *n* = 10 (9/1) 49.2 ± 10.3 years Group 2: *n* = 11 (9/2) 39.8 ± 11.9 years	NR EDSS, Group 1: 4.3 (1.4) Group 2: 1.6 (2.2) RR	Cybex leg press machine	Isotonic leg press: extension	Scaled to BW	Sit-to-stand, s
Broekmans et al. [47]	Intervention Group 1: *n* = 11 (6/5) 44.9 ± 11.6 years Group 2: *n* = 11 (6/5) 48.7 ± 8.6 years Group 3: *n* = 14 (11/3) 49.7 ± 11.3 years	NR EDSS, Group 1: 4.5 ± 1.3 Group 2: 4.4 ± 0.9 Group 3: 4.1 ± 1.1 RR/PP/SP	Biodex isokinetic dynamometer	Isometric/isokinetic Knee: extension (45/90, 60/s), flexion (45/90) Both (mean)	MVIC/MVDC, Nm	FR (functional reach), cm
Broekmans et al. [32]	Cross-sectional *n* = 52 (36/16) 47.2 ± 1.4 years	17.9 ± 1.1 years EDSS: 4.4 ± 0.2 RR/PP/SP	Biodex isokinetic dynamometer	Isometric/isokinetic Knee: extension (45/90, 60/s), flexion (45/90) Both (mean)	MVIC/MVDC, Nm	T25FWT, s TUG, s 2MWT, m
Broekmans et al. [48]	Intervention Group 1: *n* = 11 (7/4) 46.1 ± 2.1 years Group 2: *n* = 14 (11/3) 49.7 ± 3.3 years	NR EDSS Group 1: 4.5 ± 0.4 Group 2: 4.1 ± 0.3 RR/PP/SP	Biodex isokinetic dynamometer	Isometric/isokinetic Knee: extension (45/90, 60/s), flexion (45/90) Right	MVIC/MVDC, Nm	BBS, score
Callesen et al. [14]	Cross-sectional *n* = 90 (65/25) 49.8 ± 10.5	9.5 (1.5–17.4) EDSS = 3.7 ± 1.3 RR/PP/SP	Cybex Norm isokinetic dynamometer	Isometric Knee: extension (70°) Flexion (30°) Ankle: plantarflexion Dorsiflexion Both	MVIC, Nm	6MWT, m T25FWT, s SSST, s
Chua et al. [49]	Cross-sectional *n* = 10 (8/2) 50.6 (38–57) years	NR NR NR	Force transducer	Isokinetic Hip and ankle: flexion and extension	MVDC, Nm	T25FWT, s BBS, score

Table 1 (*Continued*)

Authors	Study characteristics			Muscle mechanical function		Functional capacity tests
	Study type Sample size (*n*, women/men) Age (years)	Time since diagnosis (years) EDSS/PDDS score Type of MS (RR, SP, PP)	Testing device	Contraction type Joint: movement Leg	Strength outcome	Lower-limb functional capacity outcomes
Citaker et al. [50]	Cross-sectional *n* = 47 (45/2) 36.9 ± 8.4 years		Handheld dynamometer	Isometric Hip: flexion, extension, adduction, abduction Knee: flexion, extension Ankle: dorsiflexion Dominant	MVIC, N	One-leg standing balance, s
Claerbout et al. [51]	Intervention Group 1: *n* = 17 (11/6) 47.6 ± 8.3 years Group 2: *n* = 14 (6/8) 43.8 ± 12.6 years Group 3: *n* = 16 (4/12) 39.1 ± 8.2 years	Group 1: 10.3 ± 8.4 years Group 2: 12.5 ± 9.1 years Group 3: 12.1 ± 9.2 years EDSS Group 1: 5.2 ± 1.1 Group 2: 5.1 ± 1.2 Group 3: 5.3 ± 1.3 NR	Handheld dynamometer	Isometric (break method) Hip: gluteus medius Knee: quadriceps, hamstrings Ankle: tibialis anterior Both (mean)	MVIC, Nm	TUG, s 3MWT, m BBS
Coote et al. [52]	Intervention Group 1: *n* = 10 (6/4) 51.8 ± 12.1 years Group 2: *n* = 15 (11/4) 51.8 ± 12.6 years	Group 1: 12.2 ± 4 years Group 2: 11.8 ± 5.5 years NR RR/PP/SP	Handheld dynamometer	Isometric Hip: extension Knee: extension NR	MVIC, N	TUG, s BBS MSWS-12
Costantino et al. [53]	Intervention *n* = 40 (38/2) 45.4 ± 6.5 years	NR EDSS ≤ 4.0 (3.37 ± 1.26) NR	Biodex isokinetic dynamometer	Isokinetic Knee: extension, flexion (90/s–5 rep., 180/s–10 rep.) Both (compared)	MVDC, Nm	6MWT, m
Dalgas et al. [41]	Intervention Group 1: *n* = 16 (6/10) 49.1 (44.6–53.6) years Group 2: *n* = 15 (5/10) 47.7 (41.9–53.4) years	Group 1: 8.1 (4.9–11.3) years Group 2: 6.6 (3.3–9.8) years EDSS, Group 1: 3.9 (3.5–4.4) Group 2: 3.7 (3.2–4.2) RR	Biodex isokinetic dynamometer	Isometric Knee: extension, flexion (70) Best functioning	MVIC, Nm	CST, s SCT, s 10MWT, s 6MWT, m
Dodd et al. [54]	Intervention Group 1: *n* = 36 (26/10) 47.7 ± 10.8 years Group 2: *n* = 35 (26/9) 50.4 ± 9.6 years	NR NR RR	Single seated leg press Single reverse leg press	Isotonic Leg press (1RM, resistance) Both	MVDC, kg	2MWT, m Fast walk speed, m/s
Fritz et al. [22]	Cross-sectional *n* = 29 (17/12) 48.69 ± 11.46 years	11.9 (8.6) years EDSS = 4.0 (1.0–6.5) NR	Handheld dynamometer	Isometric Hip: flexion, extension, abduction Both (sum)	MVIC, lb	Walk velocity (instrumented walkway) TUG, s T25FWT, s 2MWT, m
Guclu-Gunduz et al. [55]	Intervention Group 1: *n* = 18 (NR) 36 (29–40) years Group 2: *n* = 8 (NR) 36 (27.7–45.2) years	Group 1: 2 (1.3–7.6) years Group 2: 1.75 (0.6–3.7) years EDSS Group 1: 2 (0.75–3.5) Group 2: 1.75 (1.3) NR	Handheld dynamometer	Isometric Hip: flexion, extension, adduction, abduction Knee: flexion, extension Ankle: dorsiflexion NR	MVIC, lb	BBS TUG, s
Guerra et al. [56]	Cross-sectional *n* = 17 (13/4) 47.8 ± 10.6 years	6.8 ± 5.1 years EDSS = 1.5–4.5 RR/SP	Load cell	Isometric Knee: extension Both	MVIC, kg	BBS 6MWT, m
Güner et al. [23]	Cross-sectional Group 1: *n* = 22 (NR) 29.7 ± 5.2 years Group 2: *n* = 7 (NR) 37.5 ± 7.2 years	NR EDSS, Group 1: 1.0–4.5 Group 2: > 4.5 NR	Biodex isokinetic dynamometer	Isokinetic Knee: extension, flexion (60/s) Both (min, max)	MVDC, Nm	Velocity (3D Gait analysis), m/s

Table 1 (*Continued*)

Authors	Study characteristics			Muscle mechanical function		Functional capacity tests
	Study type Sample size (*n*, women/men) Age (years)	Time since diagnosis (years) EDSS/PDDS score Type of MS (RR, SP, PP)	Testing device	Contraction type Joint: movement Leg	Strength outcome	Lower-limb functional capacity outcomes
Hameau et al. [57]	Cross-sectional *n* = 30 (18/12) 48.06 ± 9.99 years	10.7 ± 6.82 years EDSS = 3.75 (3.55) RR/PP/SP	ConTrex-MJ isokinetic dynamometer	Isometric Knee: extension, flexion (90) Weakest leg	MVIC, Nm Fatigue Index	6MWT, m 10MWT–, s TUG, s ST, s
Hansen et al. [58]	Cross-sectional *n* = 24 (12/12) 47 ± 11 years	11 ± 8 years EDSS = 3.1 ± 1.2 RR/PP/SP/PR	Biodex isokinetic dynamometer	Isometric Knee: extension, flexion (90) Both	MVIC, Nm	6MWT, s
Hayes et al. [59]	Intervention *n* = 19 (11/8) 48.9 ± 11.14 years	12.15 ± 8.12 years EDSS = 5.24 ± 0.96 NR	Strain gauge	Isometric Hip: flexion, extension Knee: flexion, extension Ankle: dorsiflexion Both	MVIC, kg	TUG, s 10MWT, m/s ST, s 6MWT, m BBS
Jensen et al. [60]	Intervention Group 1: *n* = 19 (12/7) 48.4 ± 6.4 years Group 2: *n* = 16 (7/9) 50.8 ± 0.8 years	Group 1: 9.8 ± 5.9 years Group 2: 9.5 ± 5.4 years EDSS Group 1: 5.5 ± 0.7 Group 2: 5.8 ± 0.8 NR	Isokinetic dynamometer	Isometric, Isokinetic Knee: extension flexion (70°, 30°/s, 180°/s) Hip: flexion (20°, 30°/s, 180°/s) Both	MVIC, Nm MVDC, Nm RFD Nm/s	T25FWT, s 5 Sit-to-Stand, s SSST, s
Kalron et al. [24]	Cross-sectional *n* = 52 (36/16) 35.2 ± 7.2 years	54.0 ± 34.7 years EDSS = 1.7 ± 1.3 (5) CIS	Cybex isokinetic dynamometer	Isometric Knee: flexion (60), extension (45) Ankle: plantarflexion, dorsiflexion Both	MVIC, Nm	Velocity (GaitRite system), cm/s
Kalron et al. [25]	Intervention Group 1: *n* = 24 (16/8) 34.0 ± 2.0 years Group 2: *n* = 25 (17/8) 35.6 ± 1.5 years	< 2 months EDSS Group 1: 2.0 ± 0.2 Group 2: 1.4 ± 0.2 CIS	Cybex isokinetic dynamometer	Isometric Knee: flexion (60), extension (45) Ankle: plantarflexion, dorsiflexion Both	MVIC, Nm	Velocity (GaitRite system), cm/s
Ketelhut et al. [61]	Cross-sectional *n* = 34 (26/8) 53.8 ± 12.4 years	13.7 ± 8.6 years PDDS = 2 (0.6) RR/SP	Force transducer	Isometric Knee: flexion, extension (90°) Both	MVIC, N/kg	T25FWT, m/s TUG, s Sit-to-Stand, s
Kierkegaard et al. [44]	Intervention *n* = 20 (16/4) 36.3 ± 7.6 years	5.4 ± 3.4 years EDSS = 1.5 (1.0–2.4) RR	1 RM Biodex dynamometer	Isotonic, Isokinetic Knee: extension, flexion (60°/s, 90°/s) Both	1 RM, kg MVDC, Nm	Sit-to-Stand, s 10MWT, m/s, s
Kjølhede et al. [10,42]	Cross-sectional/intervention *n* = 35 (26/8) 43.3 ± 8.2 years	NR EDSS = 2.9 ± 0.7 RR	Humac Norm isokinetic dynamometer	Isometric, isokinetic Knee: extension (70°, 60°/s) Flexion (20°, 60°/s) Both	MVIC, Nm/kg MVDC, Nm/kg RFD Nm/kg/s	T25FWT, m/s 2MWT, m/s 5 Sit-to-Stand, s Stair climb, s MSWS12
Klaren et al. [62]	Cross-sectional *n* = 59 (42/17) 52.0 ± 7.8 years	13.1 ± 8.7 years EDSS = 4.0 ± 2.5 RR/PP/SP	Biodex, dynamometer	Isometric Knee: extension	MVIC, Nm	T25FWT, s
Lee Y et al. [63]	Intervention *n* = 6 (5/1) 55.3 ± 11.2 years	16.0 ± 6.5 years EDSS = 5.2 ± 2.5 NR	Dynamometer	Isometric Ankle: plantarflexion, dorsiflexion NR	MVIC, Nm	6MWT, m 10MWT, s TUG, s BBS

Table 1 (*Continued*)

Authors	Study characteristics			Muscle mechanical function		Functional capacity tests
	Study type Sample size (*n*, women/men) Age (years)	Time since diagnosis (years) EDSS/PDDS score Type of MS (RR, SP, PP)	Testing device	Contraction type Joint: movement Leg	Strength outcome	Lower-limb functional capacity outcomes
Mañago et al. [15,64]	Cross-sectional *n* = 72 (60/12) 47.6 ± 11.3	10.3 ± 8.6 EDSS = 3.5 ± 1.1 NR	Handheld dynamometer	Isometric Knee: flexion, extension Hip: flexion, extension, abduction, adduction Ankle: dorsiflexion Trunk: lateral flexion Weaker	MVIC, kg/BMI	T25FWT, s 6MWT, m
Manca et al. [40]	Intervention *n* = 20 (15/5) 45 ± 10.3 years	14.9 ± 8.5 years EDSS = 3.0 ± 1.0 RR	Biodex dynamometer	Isokinetic Ankle: dorsiflexion (10°/s, 45°/s) Stronger	MVDC, Peak moment, Nm	2MWT, m 6MWT, m 10MWT, s TUG, s
McLoughlin et al. [65,66]	Cross-sectional *n* = 34 (26/8) 49.1 ± 10.4 years	8.2 ± 7.9 years EDSS = 3.5 (3–6) NR	Strain gauge	Isometric Knee: extension Ankle: dorsiflexion NR	MVIC, kg	6MWT, m
Moller et al. [30]	Cross-sectional Group 1: *n* = 11 (6/5) 48.2 ± 10.2 years Group 2: *n* = 11 (4/7) 50.0 ± 13.3 years	NR EDSS, Group 1: 3.3 ± 0.9 Group 2: 4.3 ± 1.6 RR/PP/SP	Humac Norm, Isokinetic dynamometer	Isokinetic, isometric Knee: extension (60°/s, 70°) Flexion (60°/s, 30°) Hip: extension, flexion (45°) Both	MVIC, MVDC, Nm	5 Sit-to-Stand, s
Moradi et al. [67]	Intervention Group 1: *n* = 8 (0/8) 34.38 ± 11.07 years Group 2: *n* = 10 (0/10) 33.13 ± 7.08 years	Group 1: 8.12 ± 4.79 years Group 2: 6.5 ± 5.78 years EDSS Group 1: 3 (1–6) Group 2: 3 (1–5) RR/SP	Leg extensor Leg press	Isotonic Knee: extension Hip and knee: extension (–12 RM)	1 RM (predicted by the ACSM equation from 619 reps), kg	10MWT, s 3-minute step, n of rep. TUG, s Flamingo Stand Test for balance, s
Ng et al. [28]	Cross-sectional *n* = 16 (11/5) 47 ± 1 years	NR EDSS = 3.2 (1.5–6) NR	Force transducer	Isometric Ankle: dorsiflexion Right	MVIC, N RFD, %	T25FWT, s
Patrocinio de Oliveira et al. [43]	Intervention Group 1: *n* = 21 (16/6) 50.6 ± 9.3 years Group 2: *n* = 31 (18/13) 46.0 ± 11.7 years	Group 1: 11.7 ± 8.5 years Group 2: 11.0 ± 7.6 years EDSS Group 1: 3.9 ± 1.2 Group 2: 3.3 ± 1.4 RR/PP/UN	Strain gauge 1 RM, extensor	Isometric, isotonic Knee: extension Both	MVIC, kg 1RM, kg	TUG, s Chair-Stand test (Rikli and Jones protocol), s
Pilutti et al. [68]	Cross-sectional *n* = 64 (46/18) 52.0 ± 7.8 years	13.2 ± 8.8 years EDSS = 4.25 ± 2.5 RR (77.4%)	Biodex dynamometer	Isometric Knee: extension, flexion Both (mean)	MVIC, Nm	T25FWT, m/s 6MWT, m
Proessl et al. [36]	Cross-sectional *n* = 19 (12/7) 53.7 ± 9.6	14.2 ± 8.1 PDDS = 3 (0–6) NR	Force transducer	Isometric Knee: extension Both	Symmetry index (%)	6MWT, m and DWI
Ramari et al. [69]	Cross-sectional *n* = 28 (28/0) 33.9 ± 9.2 years	4.9 ± 3.9 years EDSS = 2.5 (1–3) RR	Biodex dynamometer	Isokinetic Knee: extension, flexion (60°/s, 90°/s, 180°/s) Both	MVDC, Nm	6MWT, m and DWI
Ratchford et al. [26]	Intervention *n* = 5 (2/3) 50 (46–60) years	13 (6–21) years 6.5 (6.0–6.5) years SP/PP	Handheld dynamometer	Isometric Knee: flexion, extension Hip: flexion, extension Ankle: dorsiflexion NR	MVIC, lb	T25FWT, s GaitRite, velocity, m/s 2MWT, m TUG, s

Table 1 (*Continued*)

Authors	Study characteristics			Muscle mechanical function		Functional capacity tests
	Study type Sample size (*n*, women/men) Age (years)	Time since diagnosis (years) EDSS/PDDS score Type of MS (RR, SP, PP)	Testing device	Contraction type Joint: movement Leg	Strength outcome	Lower-limb functional capacity outcomes
Samaei et al. [70]	Intervention Group 1: *n* = 17 (14/3) 33.9 ± 7.3 years Group 2: *n* = 17 (14/3) 32.1 ± 7.6	Group 1: 4.8 ± 3.3 years Group 2: 4.5 ± 2.8 years NR NR	Biodex isokinetic dynamometer	Isometric Knee: extension and flexion (30°, 60°, 90°) Both	MVIC, Nm	TUG, s T25FWT, s 2MWT, m
Sandroff et al. [6]	Cross-sectional *n* = 31 (27/4) 43.4 ± 7.7 years	8.6 ± 6.3 years PDDS = 2 (0–5) RR (93.5%)	Humac Norm Isokinetic dynamometer	Isometric Knee: extension, flexion Both	Symmetry index (%)	T25FWT, s 6MWT, ft GaitRite, velocity, cm/s MSWS12
Sandroff et al. [71]	Cross-sectional *n* = 63 (45/18) 52.2 ± 7.8 years	13.2 ± 8.8 years EDSS = 4.5 (1.5–6.5) RR/PP/SP/UN	Biodex isokinetic dynamometer	Isometric Knee: flexion (45°, 60°, 75°) Both	MVIC, Nm	T25FWT, s 6MWT, m GaitRite, velocity, cm/s
Sangelaji et al. [72]	Intervention Group 1: *n* = 10 (NR) 35.8 ± 8.4 years Group 2: *n* = 10 (NR) 31.3 ± 8.2 years Group 3: *n* = 10 (NR) 33.9 ± 7.9 years Group 4: *n* = 10 (NR) 33.6 ± 6.9 years	2 years EDSS Group 1: 1.3 ± 0.6 Group 2: 2.0 ± 0.8 Group 3: 1.9 ± 1.1 Group 4: 1.8 ± 0.5 RR	1 RM, Leg extension and Leg flexion	Isotonic Knee: extension, flexion Both	1 RM, kg	10MWT, m/s 2MWT, m/s BBS, score 6MWT, m
Schwid et al. [73]	Cross-sectional *n* = 20 (NR) 47.9 ± 7.4 years	15.3 ± 7.7 years EDSS = 5.5 ± 1.3 NR	Force transducer	Isometric Hip: flexion, Knee: flexion, extension Ankle: dorsiflexion Dominant	MVIC, N	8MWT, s 500MWT, s
Schyns et al. [74]	Intervention Group 1: *n* = 5 (NR) 45.8 ± 8.4 years Group 2: *n* = 7 (NR) 49.5 ± 6.14 years	Group 1: 6.7 years Group 2: 11.8 years NR NR	Handheld dynamometer	Isometric Hip: flexion, extension, adduction, abduction Knee: flexion, extension Ankle: dorsiflexion Dominant	MVIC, (delta)	10MWT, s TUG, s
Surakka et al. [75]	Intervention Group 1: *n* = 30 (30/0) 43 ± 6 years Group 2: *n* = 17 (0/17) 45 ± 6 years Group 3: *n* = 31 (31/0) 44 ± 7 years Group 4: *n* = 17 (0/17) 44 ± 7 years	Group 1: 6 ± 6 years Group 2: 6 ± 7 years Group 3: 6 ± 7 years Group 4: 5 ± 6 years EDSS Group 1: 2.0 ± 0.8 Group 2: 2.9 ± 1.2 Group 3: 2.5 ± 1.0 Group 4: 3.1 ± 1.2 RR/PP/SP	Knee muscle Dynamometer	Isometric Knee: extension, flexion NR	MVIC, Nm Fatigue Index, %	500MWT, m
Taylor et al. [76]	Intervention *n* = 9 (7/2) 45.6 ± 10.7 years	6.0 ± 4.1 years NR NR	Leg press, 1RM	Isotonic Knee and hip: extension Both	1 RM, kg Muscle endurance, reps	10MWT, m/s 2MWT, m Timed stair walk (15 steps), s
Thoumie et al. [12]	Cross-sectional *n* = 100 (50/50) 47 ± 10 years	NR EDSS ≥ 6.5 NR	Cybex Norm isokinetic dynamometer	Isokinetic Knee: extension and flexion (60°/s) Both	MVDC, Nm	Locometre, gait analysis velocity, m/s

Table 1 (*Continued*)

Authors	Study characteristics			Muscle mechanical function		Functional capacity tests
	Study type Sample size (*n*, women/men) Age (years)	Time since diagnosis (years) EDSS/PDDS score Type of MS (RR, SP, PP)	Testing device	Contraction type Joint: movement Leg	Strength outcome	Lower-limb functional capacity outcomes
Uszynski et al. [77]	Intervention Group 1: $n = 14$ (10/4) 45.5 (38.5–52.3) years Group 2: $n = 13$ (13/0) 54 (45.0–61.5) years	NR NR RR/PP/SP	Biodex isokinetic dynamometer	Isokinetic Knee: extension, flexion (90°/s, 180°/s, 300°/s) NR	MVDC, Nm	TUG, s 6MWT, m MiniBEST test for Balance, Score
Wagner et al. [29]	Cross-sectional $n = 42$ (27/15) 42 ± 10 years	7.7 ± 6.2 years EDSS = 3.0 (0–6) RR/PP/SP	Biodex isokinetic dynamometer	Isometric Ankle: plantarflexion, dorsiflexion Both	MVIC, Nm/kg	T25FWT, s 6MWT, m MSWS12
White et al. [78]	Intervention $n = 8$ (7/1) 46 ± 12 years	NR EDSS = 3.7 ± 1 NR	Isokinetic dynamometer	Isometric Knee and Ankle: extension and flexion NR	MVIC, N/kg	T25FWT, s 3-minute step, n of rep.
Yahia et al. [13]	Cross-sectional $n = 20$ (10/10) 36.80 ± 6.01 years	8.44 ± 5.25 years EDSS = 2.8 ± 0.9 RR	Cybex isokinetic dynamometer	Isokinetic Knee: extension and flexion (60°/s) Both	MVDC, Nm	Bessou device for gait, velocity (10 meter walkway), km/h
Yang et al. [79]	Intervention $n = 25$ (18/7) 50.3 ± 14.1 years	15.3 ± 10.5 years PDDS = 3.58 ± 1.80 RR/SP/PR/UN	Biodex isokinetic dynamometer	Isometric Knee: extension and flexion Both	MVIC, Nm/kg	EquiScale Test, balance TUG, s

NR: non-reported; RR: relapse-remitting; SP: secondary progressive; PP: primary progressive; MVIC: maximal voluntary isometric contraction; MVDC: maximal voluntary dynamic contraction; RFD: rate of force development; RM: repetition maximum; N: Newton; Nm: Newton-meter; BMI: body mass index; BW: body weight; 6MWT: Six-Minute Walk Test; DWI: distance walked index; 2MWT: Two-Minute Walk Test; T25FWT: Timed 25-Foot Walk Test; MSWS-12: Multiple Sclerosis Walk Scale; TUG: the Timed Up and Go Test; BBS: Berg Balance Scale; CST: Chair-Stand Test; SCT: Stair Climbing Test; ST: Stair time To Ascend and Descend Test; 10MWT: Ten-Meter Walk test; SSST: Six Spot Step Test; 8MWT: Eight-Meter Walk Test; 500MWT: Five Hundred-Meter Walk Test.

Table 2
Articles reporting data on the association between lower-limb strength and functional capacity.

Authors	Limb: muscle group, velocity (position), unit	Short Walking Test	Long Walking Test	TUG	Sit-to-Stand
Almuklass et al. [27]	Weakest (W) | Strongest (S):	W | S:	W | S:		
	PF, 0°/s, Nm	**0.11** | 0.02	0.04 | 0.00		
	DF, 0°/s, Nm	**0.25** | **0.11**	**0.18** | 0.04		
Bowser et al. [16]	Both: 1RM leg press				0.10
Broekmans et al. [32]	Weakest (W) | Strongest (S):	W | S:	W | S:	W | S:	
	KE, 0°/s (45), Nm	**0.09** | **0.07**	**0.26** | **0.15**	**0.12** | **0.07**	
	KE, 0°/s (90), Nm	**0.12** | **0.18**	**0.29** | **0.28**	**0.12** | **0.16**	
	KE, 60°/s, Nm	**0.13** | **0.16**	**0.30** | **0.26**	**0.11** | **0.12**	
	KF, 0°/s (45), Nm	**0.27** | **0.12**	**0.44** | **0.21**	**0.28** | **0.10**	
	KF, 0°/s (90), Nm	**0.37** | **0.28**	**0.53** | **0.28**	**0.32** | **0.30**	
Callesen et al. [14]	Weakest (W):	W:	W:		
	KE, 0°/s (70), Nm	**0.22**	**0.18**		
	KF, 0°/s (30), Nm	**0.19**	**0.14**		
	PF, 0°/s, Nm	**0.19**	**0.21**		
	DF, 0°/s, Nm	**0.12**	**0.16**		
Güner et al. [23]	Weakest (W) | Strongest (S):	W | S:			
	KE, 60°/s, Nm	**0.40** | **0.34**			
	KF, 60°/s, Nm	**0.33** | **0.22**			
Hameau et al. [57]	Weakest (W):	W:	W:	W:	
	KE, 0°/s (90), Nm	**0.31**	**0.17**	**0.24**	
	KF, 0°/s (90), Nm	**0.21**	**0.16**	0.11	
Jensen et al. [60]	Weakest (W) | Strongest (S):	W | S:			W | S:
	KE, 30°/s, Nm	**0.09** |			
	KE, Composite, Nm	**0.25** |			| **0.25**
	KE, 0°/s, RFD (Nm/s)	| **0.25**			**0.25** |
	KF, 0°/s, RFD (Nm/s)	**0.25** |			
Kjølhede et al. [10]	Weakest (W) | Strongest (S):	W | S:	W | S:		W | S:
	KE, 0°/s (70), Nm/kg	**0.23** | **0.16**	**0.30** | **0.14**		**0.12** | 0.05
	KF, 0°/s (20), Nm/kg	**0.16** | **0.17**	**0.14** | **0.16**		0.04 | 0.07
	KE, 60°/s, Nm/kg	**0.37** | **0.20**	**0.42** | **0.20**		**0.16** | 0.07
	KF, 60°/s, Nm/kg	**0.40** | **0.33**	**0.42** | **0.32**		**0.17** | **0.13**
	KE, 0°/s, RFD, Nm/kg/s	**0.24** | **0.18**	**0.19** | 0.10		0.06 | 0.06
	KF, 0°/s, RFD, Nm/kg/s	**0.12** | 0.06	**0.11** | 0.04		0.02 | 0.01
	KE, 0°/s, RFD@200ms Nm/kg/s	**0.31** | **0.18**	**0.30** | 0.10		0.10 | 0.02
	KF, 0°/s, RFD@200ms Nm/kg/s	**0.26** | **0.17**	**0.29** | **0.12**		0.05 | 0.07
Klaren et al. [62]	Strongest (S):	S:			
	KE, 0°/s, Nm	**0.34**			
Mañago et al. [15]	Weakest (W):	W:	W:		
	KE, 0°/s, kg/BMI	**0.28**	**0.34**		
	KF, 0°/s, kg/BMI	**0.47**	**0.44**		
	HE, 0°/s, kg/BMI	**0.25**	**0.27**		
	HF, 0°/s, kg/BMI	**0.33**	**0.42**		
	HAb, 0°/s, kg/BMI	**0.47**	**0.47**		
	HAd, 0°/s, kg/BMI	**0.30**	**0.37**		
	DF, 0°/s, kg/BMI	**0.32**	**0.29**		
Moller et al. [30]	Weakest (W) | Strongest (S):				W | S:
	KE, 0°/s (70°), Nm/kg				**0.59** | 0.09
	KF, 0°/s (30°), Nm/kg				**0.36** | 0.16
	HE, 0°/s (45°), Nm/kg				0.17 | 0.01
	HF, 0°/s (45°), Nm/kg				**0.36** | 0.24
	KE, 60°/s, Nm/kg/s				**0.49** | 0.05
	KF, 60°/s, Nm/kg/s				**0.40** | 0.09
Ng et al. [28]	Right (R):	R:			
	DF, 0°/s, RFD (% peak tetanic/ms)	**0.33**			
Pilutti et al. [68]	Strongest (S):	S:	S:		
	KE, 0°/s (60), Nm (ID)	**0.33**	**0.47**		
	KF, 0°/s (60), Nm (ID)	**0.36**	**0.47**		
Sandroff et al. [71]	Strongest (S):	S:	S:		
	KF, 0°/s, Nm	**0.53**	**0.43**		
Thoumie et al. [12]	Weakest (W) | Strongest (S):	W | S:			
	KE, 60°/s, Nm	**0.15** | **0.12**			
	KF, 60°/s, Nm	**0.22** | **0.19**			
Wagner et al. [29]	Weakest (W):	W:	W:		
	PF, 0°/s, Nm/kg	**0.29**	**0.29**		
	DF, 0°/s, Nm/kg	0.06	**0.17**		
Yahia et al. [13]	Weakest (W) | Strongest (S):	W | S:			
	KE, 60°/s, Nm	**0.28** | 0.07			
	KF, 60°/s, Nm	**0.23** | **0.36**			

The R^2 values are presented for 1 or 2 limbs depending on how the results were reported in the original paper.
PF: plantar flexor; DF: dorsiflexor; KE: knee extensor; KF: knee flexor; HE: hip extensor; HF: hip flexor; HAb: hip abductor; HAd: hip adductor; RFD: rate of force development.
Bold font indicates statistical significance $P \leq 0.05$.

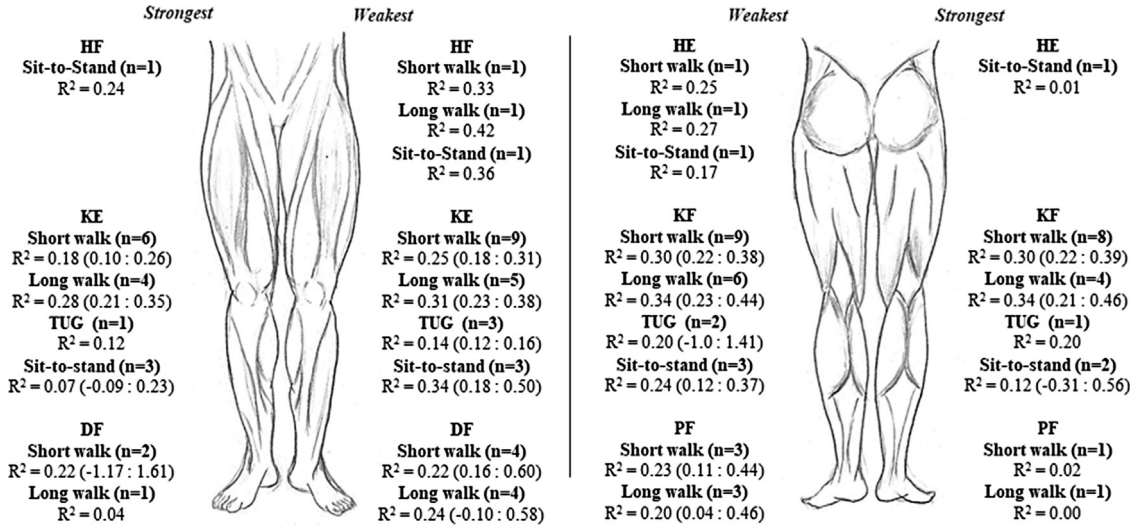

Fig. 2. Association between lower-extremity strength of different muscles divided into the strongest and weakest leg and measures of lower-limb functional capacity. The R^2 values are presented as mean and 95% confidence intervals across studies adjusted for sample size and sex ratio. In the illustration, the right leg represents the strongest leg (although it could be different in individual study participants). HF: hip flexor; HE: hip extensor; KE: knee extensor; KF: knee flexor; DF: dorsiflexor; PF: plantar flexor.

Table 3
Summary of associations between isometric (0°/s) and isokinetic (60°/s) muscle strength of the knee extensors and flexors and walking tests (short and long).

	KE				KF			
	Short		Long		Short		Long	
	Isometric	Isokinetic	Isometric	Isokinetic	Isometric	Isokinetic	Isometric	Isokinetic
	0.15 [32]	0.15 [32]	0.29 [32]	0.28 [32]	0.33 [32]	0.28 [23]	0.41 [32]	0.37 [10]
	0.31 [57]	0.38 [23]	0.18 [57]	0.31 [10]	0.21 [57]	0.21 [12]	0.18 [57]	
	0.35 [62]	0.14 [12]	0.38 [68]		0.29 [68]	0.30 [13]	0.41 [68]	
	0.27 [68]	0.18 [13]	0.48 [68]		0.36 [68]	0.37 [10]	0.48 [68]	
	0.34 [68]	0.29 [10]	0.22 [10]		0.17 [10]		0.15 [10]	
	0.20 [10]	0.09 [60]	0.18 [14]		0.53 [71]		0.44 [71]	
	0.22 [14]		0.35 [15]		0.19 [14]		0.14 [14]	
	0.28 [15]				0.48 [15]		0.45 [15]	
Adjusted mean (95% CI)	0.26 (0.19: 0.32)	0.17 (0.09: 0.26)	0.29 (0.18: 0.40)	0.30	0.30 (0.19: 0.41)	0.33 (0.14: 0.51)	0.32 (0.17: 0.47)	0.37

Data are presented as R^2 [article reference]. The mean R^2 values and their 95% confidence intervals (CIs) are adjusted for sample size and sex ratio.
KE: knee extensor; KF: knee flexor.

4. Discussion

The primary purpose of this systematic literature review was to identify studies that measured lower-extremity muscle mechanical function and lower-limb functional capacity (e.g., walking, dynamic balance and chair rise) in PwMS. Findings across studies showed that lower-extremity muscle mechanical function (predominantly muscle strength) explained a significant part of the variance in lower-limb functional capacity tests (approximately 20–30%). This was particularly evident in muscle mechanical function outcomes from the weakest leg. In addition, the most frequently reported associations were knee extensor and flexor muscle strength, which overall explained the same part of the variance in walking capacity. Overall, lower-extremity muscle mechanical function most frequently was evaluated by using isokinetic dynamometry while performing maximal isometric (0°/s) and dynamic contractions at slow contraction velocities (30–60°/s). Short walking tests such as the T25FWT and the 10-Min Walk Test were the most frequently performed functional capacity tests. Despite the large number of studies ($n = 59$) evaluating lower-extremity muscle mechanical function and lower-limb functional capacity outcomes, only a subset of these ($n = 17$) reported the association between muscle mechanical function (predominantly muscle strength) and functional capacity, which limited the number of findings that could be mapped.

4.1. Lower-extremity muscle groups and lower-limb functional capacity

The reviewed articles predominantly evaluated muscle strength of the knee extensors and flexors, generally revealing large heterogeneity between study findings. This systematic review clearly shows that testing of hip muscle strength (and to some extent plantar flexor muscle strength), and relating this to lower-limb functional capacity has not gained much attention in MS research. Møller et al. [30] reported a significant association between hip flexor muscle strength (but not hip extensor muscle strength) of the weakest leg and the Sit-to-Stand Test. In addition, Mañago et al. [15] reported significant associations between lower-extremity muscle strength from hip muscles and walking capacity. In addition to evaluation of hip flexors and extensors, Mañago et al. [15] emphasized the importance of the hip abductor and adductor muscle strength on walking performance. To compensate for weakness of major muscle groups during walking, such as the hip extensors and knee flexors, an increase in the contribution from the ankle plantar flexors has been shown,

thereby revealing the plantar flexors as an important muscle group during support, forward propulsion and swing initiation in normal walking [31]. This notion can nevertheless not be inferred from the present data because it would require a longitudinal study with multiple test sessions to examine the time course of strength changes in different (e.g., distal versus proximal) muscle groups.

Broekmans et al. [32] found stronger associations with walking capacity for knee flexor than knee extensor muscle strength in MS patients (R^2 range 0.10–0.53 vs 0.07–0.30). Previous studies [33,34] in older individuals have suggested that a non-linear S-shaped relationship exists between lower-extremity muscle strength and walking capacity (i.e., with the association wearing off when muscle strength is very low and very high, respectively). Hence, the observations by Callesen et al. [14], may reflect that the level of knee extensor (and plantar flexor) muscle strength in PwMS walking less than 400 m during the 6MWT do not affect walking capacity, whereas walking more than 400 m during the 6MWT the level of knee extensor (and plantar flexor) muscle strength do impact walking capacity. This notion did not agree with Thoumie et al. [12], where associations between knee extensor muscle strength and functional capacity did not differ between less and more disable PwMS. However, the authors reported a stronger association between knee flexor muscle strength and lower-limb functional capacity in less disabled PwMS. Taken together, the findings of the present systematic review suggest that muscle strength of both hip, knee and ankle muscle groups are related to lower-limb functional capacity in ambulatory PwMS (explaining approximately 20–30%). It is likely that the strength of the association may depend on whether the muscle group acts as an agonist or antagonist to a particular movement and whether patients are mild, moderately or severely impaired. Nevertheless, the latter was not supported by data from the present study in that EDSS score did not affect the associations between lower-extremity muscle strength and walking capacity (data not shown). This may have been due to the narrow range of EDSS scores (i.e. from 2.8 to 6.5) along with the heterogeneity in lower-limb functional capacity tests across the included studies.

4.2. Strongest versus weakest limb

An interesting finding of the present study was the stronger relationships between lower-extremity muscle mechanical function and lower-limb functional capacity outcomes observed in the weakest versus the strongest leg. Intuitively this makes sense, because the weaker leg would likely be more limiting to lower-limb functional capacity than the stronger leg. Defining the weakest leg can nevertheless be difficult because some muscle groups may be stronger in one leg, whereas other muscle groups are stronger in the other leg. Moreover, an affected leg following a relapse may still be stronger than the non-affected leg. Keeping that in mind, the most direct approach is by establishing the degree of muscle strength asymmetry between legs (i.e., by testing both legs and calculating the percentage difference). Studies suggest clinically important strength asymmetries if the difference exceeds 10% [33], which is a clinical cut-off point that could be applied to more appropriately investigate the effects of the lower-extremity muscle strength asymmetry in functional capacity of PwMS. Leg asymmetry has been shown to be associated with walking capacity in PwMS (i.e., with slower walking speed and T25FWT [6,35]), but Proessl et al. [36] did not find associations between knee extensor strength asymmetry and walking ability and fatigability in PwMS. Also, a study from Kalron et al. [37] revealed no incidence of asymmetry of the vertical ground reaction force during gait in PwMS along with no association with walking and balance. As suggested in MS studies, the weaker leg and the resulting asymmetry in lower-extremity muscle strength likely lead to decreased performance during lower-limb functional capacity tests. This situation may be due to the need for equivalent force production by the knee extensor and flexor muscles to perform symmetrical movements to lower the energy cost [33]. In this way, in PwMS, the stronger leg may lower its strength production to equate with the weaker leg, thereby leading to an overall decrease in functional capacity performance over time. Another theory may relate to the stronger leg trying to compensate for the weaker leg, which over time could further increase the gap between the legs. However, it does seem that the weakest "link of the chain" is the main determinant of lower-limb functional capacity, making it less likely that the strongest leg can fully compensate for the weaker leg. Also of note, the results from this review suggest that the Sit-to-Stand Test was the most sensitive functional capacity measurement of knee muscle strength disparity. The walking tests also revealed a strength difference between the plantar flexors, but only one article reported the R^2 value for the strongest leg.

4.3. Dynamic versus isometric contractions

As shown in this review, lower body muscle strength in most cases explains 20% to 30% of the performance in lower-limb functional capacity tests. Of note, the present review did not find any major difference between the relationship of isometric (0°/s) or dynamic (60°/s) muscle strength and lower-limb functional capacity tests in PwMS, the former being most frequently reported. An obvious explanation is that dynamic muscle contractions were performed at a rather slow velocity (i.e., 60°/s), whereas most physical tasks performed maximally may require moderate-to-fast velocity muscle contractions (i.e., $> 60°/s$). Moreover, impairments in lower-extremity muscle strength (also including "explosive" strength) and power have been shown to be much more pronounced during fast concentric muscle contractions as compared with both slow concentric, isometric and eccentric contractions [8]. We did not identify any studies examining the relationship between lower-extremity muscle power and lower-limb functional capacity, but knee extensor and knee flexor RFD (based on 3 studies only) appeared to display similar relationships to walking capacity as isometric and dynamic muscle strength. The latter has also been observed in a large-scale cohort study of older individuals [34]. Studies examining relationships between lower-extremity muscle RFD or power and lower-limb functional capacity in PwMS are thus clearly warranted.

4.4. Clinical implications

On the basis of the included cross-sectional studies, the relationships between lower-extremity muscle mechanical function and lower-limb functional capacity in PwMS suggest that a PwMS can improve lower-limb functional capacity by improving lower-extremity muscle strength or vice versa (i.e., when undergoing disuse or detraining). Indeed, studies have shown that rehab- or exercise-induced improvements in lower-extremity muscle strength translates into improvements in functional capacity tests assessing walking [38], TUG [39,40], sit-to-stand and stair climbing [41–43]. This suggests a causal relationship, in which lower-extremity muscle mechanical function is a modifiable factor that directly influences lower-limb functional capacity in PwMS. Among the many different types of rehab/exercise interventions, the most robust results were from studies evaluating high-intensity progressive resistance training (PRT) [42]. Indeed, 6 to 24 weeks of high-intensity PRT has been shown to elicit muscle strength improvements in ankle dorsiflexors [40], knee extensors [41,42,44] and flexors [41,44] that were translated into functional capacity improvements and particularly walking performance [40–42,44]. An interesting observation from the

study by Kjølhede et al. was that some of the strength exercises were performed unilateral, ultimately generating more neuromuscular and strength adaptations in the weakest leg [42]. This relates well to findings of the present review showing that the weakest leg is stronger associated to functional performance.

Our overall interpretation of the present findings, which most frequently investigated the association between knee extensor or flexor muscle strength and walking capacity, is that no lower-extremity muscle group is the main driver of lower-limb functional capacity. Hence, we would recommend that rehab/exercise interventions target all lower-extremity muscle groups acting over the ankle, knee, and hip joint. If known, the weakest leg could be specifically targeted by additional unilateral exercises. Moreover, it seems prudent to address aspects other than high-intensity PRT, for instance by involving elements that target motor control and balance. Indeed, recent studies have provided evidence that force steadiness (i.e., force fluctuations during submaximal contractions ≈ motor control) of the ankle plantar flexor and dorsiflexor muscles [27,45] along with lower-limb balance [14] also influences walking performance in PwMS. Altogether, we would recommend that high-intensity PRT serve as the core of rehab/exercise interventions supported by the other aspects, to improve lower-limb functional capacity in PwMS.

4.5. Methodological considerations

A number of methodological considerations have to be kept in mind when interpreting the results of the present review. First, all the studies reporting associations used a cross-sectional study design, which does not allow conclusions on causality and on the direction of the relationship. Second, heterogeneous studies in terms of MS populations (comprising relapse-remitting, primary progressive and secondary progressive MS types along with differences in MS disease severity), strength testing with different equipment (handheld and isokinetic dynamometry), different strength outcomes (e.g., peak torque, power and RFD), and different functional capacity tests, limit direct comparison across the included studies.

5. Conclusion

In PwMS, lower-extremity muscle strength of the weakest limb explains 20% to 30% of the performance in functional capacity tests comprising walking and sit-to-stand, independent of lower-extremity muscle group, contraction type and velocity. Exercise programs for PwMS should focus on increasing muscle mechanical function and on exercises that could minimise strength asymmetry between limbs.

Funding

This work was partially funded by the Coordination for the Improvement of Higher Education (CAPES, Brazil – Finance Code 001).

Disclosure of interest

CR and ACD declare that they have no competing interest. LGH has received research support, travel grants and/or teaching honoraria from Biogen and Sanofi Genzyme. UD has received research support, travel grants and/or teaching honorary from Biogen Idec, Merck Serono, Novartis, Bayer Schering and Sanofi Aventis as well as honoraria from serving on scientific advisory boards of Biogen Idec and Genzyme.

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Multiple Sclerosis and Related Disorders 20 (2018) 181–185

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Knee flexor strength and balance control impairment may explain declines during prolonged walking in women with mild multiple sclerosis

Cintia Ramari[a,*], Andréa G. Moraes[a], Carlos B. Tauil[b,c], Felipe von Glehn[d], Robert Motl[e], Ana C. de David[a]

[a] Faculty of Physical Education, University of Brasília, DF, Brazil
[b] Base Hospital, Department of Neurology, Brasília, DF, Brazil
[c] Faculty of Medicine, University of Brasília, DF, Brazil
[d] Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[e] Department of Physical Therapy, University of Alabama at Birmingham, AL, United States

ARTICLE INFO

Keywords:
Six-minute walking
Distance-walked-index
Strength
Balance
Multiple sclerosis
Relapsing-remitting

ABSTRACT

Background: Physiological factors such as muscle weakness and balance could explain declines in walking distance by multiple sclerosis (MS) patients. The purpose of this study was to characterize levels and examine associations among decline in walking distance, balance and muscular strength in women with mild MS.
Methods: Participants included 28 women with mild relapsing-remitting MS and 21 women without MS. We executed the 6-min walk test (6MWT) to verify declines in walking distance. Isokinetic knee flexion (KF) and extension (KE) muscle strength was measured using a dynamometer. Balance was quantified using a force platform, with eyes open and closed, on a rigid and foam surface.
Results: The MS patients presented declines in walking, lower KF muscle strength, and worse balance than controls. KF strength and balance correlated with walking in the MS group. The KF strength explained differences between groups in walking. The KF strength and balance presented as predictors of walking slowing down in the 6MWT, in mild MS.
Conclusion: Women with mild MS have strength impairment of knee flexor muscles and balance control impairment that may explain walking related motor fatigability during prolonged walking.

1. Introduction

Multiple sclerosis (MS) is a chronic disabling disease that is seemingly trigged by environmental factors in genetically susceptible people. MS most frequently occurs among young and middle-aged women of European descendent and presents with a relapsing-remitting (RRMS) course in approximately 85% of cases (Milo and Kahana, 2010). One recent systematic review (Vasconcelos et al., 2016) reported that predictors of long-term disability in the Brazilian population further were similar with Caucasian populations. Concerning symptomatic manifestations, motor disorders were most frequent (36%) in Brazilians with MS followed by sensory (27%).

Regarding motor disorders, walking performance over longer distances, such as 6-min walk test (6MWT), provide assessment of walking fatigability, maximal walking distance, and functional capacity (Kieseier and Pozzilli, 2012) and predict declines in everyday activities such as habitual walking (Pilutti et al., 2015). The 6MWT is one of the best characterized measures of walking endurance in persons with MS (Goldman et al., 2008, 2010; Pilutti et al., 2013). Persons with MS have reduced 6MWT performance compared with matched controls (Sandroff et al., 2013, 2015), and this reduction may be associated with lower extremity strength and postural control (i.e., balance) (Güner et al., 2015; Kjølhede et al., 2015; Yahia et al., 2011; Broekmans et al., 2013). In addition, recent studies suggest the importance in identify factors, such as muscle weakness and others MS related symptoms – spasticity, cerebellar signs, and sensory integration in balance, in order to explain declines in walking distance and possible altered pacing strategy adopted by MS patients (Leone et al., 2016).

This study (*1*) characterized walking capacity, balance and muscular strength in women with mild RRMS, (*2*) examined the percentage change in distance walked in the 6MWT, and its associations between muscular strength, and postural control, and (*3*) investigated possible

* Correspondence to: Faculty of Physical Education, University of Brasília, Campus Universitário Darcy Ribeiro - Asa Norte - Brasília-DF, Faculdade de Educação Física – Postal Code: 70910-970, Brazil.
E-mail addresses: cintiaramari@yahoo.com.br, cintiaramarif@gmail.com (C. Ramari), andreafisiounb@gmail.com (A.G. Moraes), cbtauil@gmail.com (C.B. Tauil), fvonglehnsilva@bwh.harvard.edu (F. von Glehn), robmotl@uab.edu (R. Motl), anacdavid@unb.br (A.C. de David).

https://doi.org/10.1016/j.msard.2018.01.024
Received 9 November 2017; Received in revised form 17 January 2018; Accepted 25 January 2018

physiological deconditioning predictors of walking impairment in persons with mild MS, based on lower limb strength and balance impairment. Such research is important for identify factors from strength and balance which could predict walking variabilities in persons with mild disability MS. From that, is important for establishing the basis of rehabilitation interventions that focus on exercise training as an approach for improving mobility in patients with MS.

2. Methods

Participants included 28 women with MS and 21 women without MS who were matched on age, height, weight, and self-reported habit of physical activity by answering questions about engagement in systematized programs of physical exercise. We obtained the written informed consent prior to procedures and the Ethics Committee from the Department of Health/Federal District – Brazil approved this project, with the protocol number: 67098217.5.0000.5553. Inclusion criteria were (*1*) aged 18 years or older; (*2*) diagnosis of relapsing-remitting (RR) MS course; (*3*) ambulatory and capable to complete the 6MWT; (*4*) relapse free over the past 30 days; and (*5*) mild MS disability as evidenced by a rating on the Expanded Disability Status Scale (EDSS) between 1 and 3. Exclusion criteria were (*1*) unable to understand the motor tests commands; (*2*) non-controlled chronical medical conditions, such as hypertension, diabetes and cardiac conditions; and (*3*) neurologic conditions in addition to MS.

2.1. Walking functional capacity

In the 6MWT participants were instructed to walk as fast and as far as possible without rest or encouragement for 6 min. The 6MWT was completed within a single corridor measuring ten-meter in length, with cones placed on opposite ends, while performing 180° turns around the cones (Sandroff et al., 2014). We placed two photocells (Cefise - Speed Test Fit, Brazil) on the corridor in order to note the distance traveled minute-by-minute.

2.2. Muscular strength

We measured the dynamic isokinetic muscle strength by an isokinetic dynamometer (Biodex Medical Systems 3, Inc., USA). The range of motion was kept within 0–80° for the knee joint. Bilateral isokinetic (concentric/concentric) flexion and extension of the knee at 60°/s, 90°/s and 180°/s was performed four times. Patients had two minutes of rest between the series and verbal encouragement was standardized.

2.3. Balance

Balance was based upon the displacement of the center of pressure (COP) quantified using a force platform (AccuSway Plus, AMTI Inc, USA). Subjects were asked to stand upright barefoot on the force platform with heels separated by 3 cm. During testing with the eyes open subjects looked at point located at the distance of 1.5 m. The data were acquired during 30-second with open and closed eyes on a rigid and on an unstable surface with a plastic foam. Participants executed three trials of each condition with 60 s of rest interval. COP velocity (COP-vel) and area of 95% ellipse (COP-area) were recorded with a sample frequency of 100 Hz, and a Butterworth digital filter with cutoff frequency of 10 Hz was used.

2.4. Data analysis

All data analyses were performed in the SPSS program (SPSS 13.0, SPSS Inc., USA). The Shapiro-Wilk test examined the normality of the data. Regarding between-group comparison, the student's *t*-test for independent samples were conducted and, the Mann-Whitney test were executed on COP-area outcomes. Analysis of variance (ANOVA) with repeated measures was conducted for examining group differences on peak torque and COP-vel. Where necessary, Tukey's post-test was conducted. For the COP-area, the Friedman test was used followed by the Wilcoxon test. To measure the decline in distance walked, we calculated the percentage change in distance walked – distance walked index (DWI), starting from the second minute (Leone et al., 2016). The DWI was calculated using the following equation:

$$DWI = \frac{Distancewalkedatminuten - Distancewalkedatminute\ \ 1}{Distancewalkedatminute\ \ 1}\ x\ 100$$

We calculated the DWI in each minute of the test (DWI_{2-1}, DWI_{3-1}, DWI_{4-1}, DWI_{5-1} and DWI_{6-1}). ANOVA was performed in order to investigate differences between groups, and differences between the DWI_{n-1} over the course of the 6MWT. Where necessary, Tukey's post-test was conducted. Depending on data distribution, we conducted the Pearson or Spearman correlations between the DWI_{6-1} and muscle strength and balance. We executed two types of multivariate linear regression analysis: hierarchical and stepwise. The hierarchical linear regression examine which variables accounted for group differences in the DWI_{6-1}. Group entered in the first step, and the variables from strength and balance were added in the step 2 and 3, respectively. To examine if a combination of predictors would explain more variance in the DWI_{6-1} for persons with MS, the variables which were significantly different between groups and had correlation with DWI_{6-1} were entered in a multivariate stepwise analysis. The level of significance adopted was 0.05.

3. Results

Demographic and clinical values are presented in Table 1. There were no significant difference in age, height and weight, $p > .05$, between groups. All patients with MS had a RRMS disease course with a short disease duration and mild level of disability based on EDSS scores.

As shown in Fig. 1, there is a significant slowing down over the course of the 6MWT by MS patients. Controls did not present any significant difference over time regarding the DWI. The analysis between groups revealed a significant statistical difference at minute 6 (adjusted p-value = .019), with higher negative percentage change in the DWI_{6-1} presented by the MS population. Persons with MS walked significantly less compared to controls in the 6MWT, see Table 2.

Regarding knee muscle strength, the results (Table 2) reveled differences between groups in the knee flexion (KF) peak torque. At 60°/s velocity, persons with MS achieved lower values of KF strength for both legs. At 90°/s velocity, the MS patients showed lower strength in the KF muscle of the left leg. Whereas the KF of the right leg achieved a lower value of peak torque at 180°/s velocity.

As indicated in Table 2, persons with mild MS had higher values of COP-vel and area compared to controls. However, the differences occurred in the rigid surface with eyes closed and in the foam surface with eyes open, with $p < .05$.

The bivariate correlations revealed associations between KF peak torque 60°/s and DWI_{6-1} (*Pearson* correlation coefficient, $R = 0.50$, $p < .05$), and between KF peak at 180°/s and DWI_{6-1} (*Pearson* correlation coefficient, $R = 0.48$, $p < .05$), only for the MS group. The

Table 1
Demographic characteristics of individuals with MS and controls without MS.

Variable	MS (n = 28)	Controls (n = 21)
Age, y	33.9 (9.2)	32.1 (7.7)
Height, cm	160.8 (5.1)	161.8 (4.7)
Weight, kg	62.2 (12.1)	60.4 (9.1)
EDSS, median (range)	2.5 (1–3)	
MS onset, y	4.9 (3.9)	
MS course	RR	

EDSS, Expanded Disability Status Scale; RR: Relapsing-Remitting.

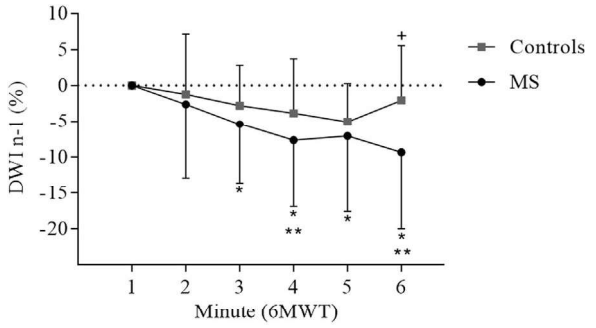

Fig. 1. The percentage Distance Walked Index (DWI_{n-1}) over time of the 6MWT. * Denotes statistical significance at $p < .05$ compared to the distance walked during minute 1 (percentage change = 0). ** Significantly different from DWI_{2-1}. $^{+}$Statistical difference ($p < .05$) between control and MS group.

DWI_{6-1} was correlated to COP-area in the foam surface with eyes closed for persons with MS (*Spearman* correlation coefficient, $R = -0.42$, $p < .05$), and to COP-area in the rigid surface with eyes open (*Pearson* correlation coefficient, $R = 0.53$, $p < .05$) for the controls.

The hierarchical regression analysis showed in the first step that the group explained 13% of the variance in the DWI_{6-1}. In the second step we included the KF strength at 60°/s ($R^2 = 0.272$), which significantly explained 14% of variance in walking. We also included the balance variables in a third step. However, this model was not significant. Suggesting that COP-vel did not contribute for walking variance explanation (see Table 3).

In the stepwise regression analysis for the MS patients, besides the variables, which were different between groups, we included the COP-area with eyes closed in the foam surface, because it was correlated with DWI_{6-1}. The stepwise retained the KF peak torque of the right leg at 60°/s, and the COP-area with eyes closed in the foam surface. With a $R^2 = 0.395$, the variables explained 39% of variance in walking performance (see Table 3).

Table 3
Summary of multiple linear regression analysis with hierarchical regression and with stepwise for predicting variance in walking.

Regression and Variables	B	SE B	β
Regression Type: *Hierarchical*			
Step 1			
Group	6.750	2.830	0.361*
Step 2			
Group	4.685	2.821	0.250
KF/RL - PT 60°/s	0.265	0.122	0.480*
KF/LL - PT 60°/s	−0.062	0.108	−0.126
Step 3			
Group	3.437	3.118	0.184
KF/RL - PT 60°/s	0.209	0.137	0.379
KF/LL - PT 60°/s	−0.017	0.118	−0.034
RS: COP-vel/EC	0.073	3.689	0.004
FS: COP-vel/EO	−2.094	2.362	−0.181
Note: $R^2 = 0.130$ for step 1 ($p < .05$); $R^2 = 0.272$ for step 2 ($p < .05$); $R^2 = 0.295$ for step 3 ($p > .05$). * Denotes statistical significance at $p < .05$.			
Regression Type: *Stepwise*			
KF/RL - PT 60°/s	0.234	0.097	0.418*
FS: COP-area/EC	−0.194	0.087	−0.389*
Note: $R^2 = 0.395$ for model. * Denotes statistical significance at $p < .05$.			

Note: KF/RL - PT 60°/s = Knee Flexion/Right Leg - Peak Torque at 60°/s; KF/LL - PT 60°/s = Knee Flexion/Left Leg - Peak Torque at 60°/s. *RS*: COP-vel/EC = *Rigid Surface*: Center of Pressure velocity/Eyes Closed; *FS*: COP-vel/EO = *Foam Surface*: Center of Pressure velocity/Eyes Open; *FS*: COP-area/EC = *Foam Surface*: Center of Pressure area/Eyes Closed.

4. Discussion

The findings of this cross-sectional study were: (*a*) women with mild MS presented a continuous slowing down over the 6MWT, lower KF

Table 2
Group differences in walking, knee muscle strength and balance.

Variable	MS	Controls	*p* value	*d* (CI)
6MWT				
Distance	506.2 (61.1)	588 (46.6)	< 0.0005*	−1.50 (−17.6 14.5)
Strength				
PT 60°/s (N-m)				
KE/RL	113.3 (26.7)	125.4 (23.8)	0.122	−0.48 (−7.75 6.78)
KE/LL	109.9 (25.7)	120.4 (25.7)	0.182	−0.41 (−7.75 6.92)
KF/RL	51.2 (17.4)	64.9 (13.9)	0.008*	−0.87 (−5.43 3.67)
KF/LL	54.2 (15.3)	67.0 (19.8)	0.019*	−0.75 (−5.73 4.22)
PT 90°/s (N-m)				
KE/RL	107.4 (27.4)	116.2 (20.1)	0.238	−0.36 (−7.35 6.61)
KE/LL	102.7 (23.8)	111.5 (21.1)	0.206	−0.39 (−6.86 6.07)
KF/RL	54.5 (17.4)	62.8 (13.8)	0.090	−0.53 (−5.07 4.01)
KF/LL	53.0 (14.2)	61.8 (10.0)	0.025*	−0.71 (−4.29 2.85)
PT 180°/s (N-m)				
KE/RL	80.6 (20.0)	89.7 (15.5)	0.104	−0.51 (−5.69 4.67)
KE/LL	76.7 (19.2)	86.0 (14.1)	0.079	−0.55 (−5.44 4.33)
KF/RL	43.7 (14.2)	52.1 (11.2)	0.037*	−0.66 (−4.36 3.03)
KF/LL	44.5 (13.4)	51.0 (8.6)	0.067	−0.57 (−3.86 2.71)
Balance				
Rigid Surface				
COP-vel/EO (cm/s)	1.0 (0.2)	0.9 (0.1)	0.222	0.62 (0.57 0.66)
COP-vel/EC (cm/s)	1.5 (0.5)	1.1 (0.1)	0.019*	1.07 (0.96 1.17)
COP-area/EO (cm^2)	3.3 (3.1)	2.0 (0.8)	0.776	0.55 (−0.09 1.20)
COP-area/EC (cm^2)	5.4 (4.5)	3.2 (1.5)	0.191	0.63 (−0.31 1.59)
Foam Surface				
COP-vel/EO (cm/s)	2.3 (0.9)	1.6 (0.2)	0.002*	1.03 (0.85 1.22)
COP-vel/EC (cm/s)	5.6 (1.9)	4.3 (1.0)	0.065	0.84 (0.41 1.27)
COP-area/EO (cm^2)	7.9 (6.1)	4.0 (1.2)	0.060	0.85 (−0.40 2.11)
COP-area/EC (cm^2)	32 (18.9)	19.4 (8.1)	0.191	0.84 (−3.26 4.96)

PT, Peak Torque; KE, Knee Extension; KF, Knee Flexion; RL, Right Leg; LL, Left Leg; COP-vel, Center of Pressure-velocity; EO, Eyes Open; EC, Eyes Closed. *d*, Cohen's d. CI, 95% confidence interval. Note: Data are presented as mean (SD). * Denotes statistical significance at $p < .05$.

muscle strength, and worse balance than controls without MS; (*b*) correlations between KF strength, balance and DWI_{6-1} in MS patients; (*c*) KF strength, but not balance, explained differences in DWI_{6-1} between MS patients and controls; (*d*) KF strength at 60°/s, and COP-area in the foam surface with eyes closed, were predictive variables which explained the variance in DWI_{6-1} among MS patients.

As shown by previous research (Sandroff et al., 2013) we demonstrated that mild MS patients walked less in the 6MWT compared to controls. There is differences between groups in DWI_{n-1}, specifically in the DWI_{6-1}. Persons with MS decelerated walking after the third minute, when compared to the first minute walked. In addition, the deceleration in the fourth and sixth minute was higher with differences from the second minute. Our findings corroborate with others studies (Dalgas et al., 2014; Gijbels et al., 2011), and suggest a pacing strategy by MS patients, reporting a faster walking speed during the first 2 min of the 6MWT. Leone et al. (2016), also reported a significant decrease in DWI_{n-1} over time from the second to the sixth minute, throughout the 6MWT, in patients with MS. The control group did not change their pacing strategy during the 6MWT, and tended to accelerate in the last minute, however the difference between DWI_{5-1} and DWI_{6-1} was not significant. In part, our study corroborate the findings from Calay et al. (2012), who suggested a mild acceleration at the end of a 500 m walking test by the healthy controls compare to mild MS patients.

There were differences in KF strength between groups. Studies suggest that muscle strength in MS is impaired (Kjølhede et al., 2015; Yahia et al., 2011; Mlk et al., 2017; Surakka et al., 2004). Our results did not identify differences between MS and controls regarding KE strength, and this is in contrast with the study of Yahia et al. (2011). A possible explanation is the differences of participant characteristics such as disease duration and biological sex. However, our finding of impairment in KF strength is consistent with the literature (Sandroff et al., 2013; Kjølhede et al., 2015; Yahia et al., 2011; Surakka et al., 2004; Citaker et al., 2013; Thoumie and Mevellec, 2002).

The differences in balance between groups were readily apparent in the rigid surface with eyes closed and in the foam surface with eyes open. All differences is concerning to COP-vel. Our results suggest that there is balance impairment associated with MS affected by the integration of sensory component. Mentel and Karpe (2010) demonstrated differences in balance between MS patients and controls in all conditions: rigid with eyes open and closed; foam with eyes open and closed. Morrison et al. (2016) also found differences between MS and controls, and they emphasized the greatest disparity during the more challenging balance tasks (i.e. when vision was withdrawn and a foam surface was used).

We found associations between peak torque values, balance and DWI_{6-1}. There was significant correlation between KF strength and DWI_{6-1} from the 6MWT only for the MS group. Yahia et al. (2011) reported significant correlation between gait parameters measured and the peak torque for the KE and KF. Kjølhede et al. (2015) reported that maximal strength was a predictor of walking performance in persons with MS. Regarding balance, the COP-area performed with eyes closed in the foam was correlated to walking capacity in the MS group. Sandroff et al. (2013) also reported bivariate correlation between COP area and 6MWT distance. However, the test was performed in a rigid surface with eyes opened.

The hierarchical regression analysis identified the KF strength as a strong predictor of group differences. Balance parameters such as COP-vel, which revealed to be different between MS and controls, did not contribute for variance between groups. Our findings corroborate the results from Sandroff et al. (2013), where that balance did not explain group differences in gait variables. The stepwise multiple linear regression analysis retained the KF peak torque at 60°/s and the COP-area from a foam surface with eyes closed in the equation. Thus, the combination of a weak KF muscle and the difficulty in control the posture in the most challenge task (foam surface with eyes closed), explained 39% of variance of the DWI_{6-1} in persons with mild disability MS. A kinematic gait analysis of patients with mild and moderate MS (Güner et al., 2015) revealed that minimum KF strength correlated highly with the peak KE moment in mild MS. Beyond that, MS patients with moderate degree had poor KF during the swing phase of the gait and the muscle strength correlated with the knee range movement. Those facts contribute to gait impairments, such as shorter swing phase, decrease of stride length and slower gait speed.

The altered sensory integration for balance control as shown by the COP-vel variable, the relation between COP-area with 6MWT and, the impairment in KF strength, suggested a possible motor compensation on walking by mild MS patients. Decrease in walking capacity, influenced by physical and sensory integration impairment, could partially influence a sedentary lifestyle that elicits multiple negative physiological changes (Mlk et al., 2017), once persons with MS seem to be less physically active than controls (Blikman et al., 2015). The literature shows that sedentary time is associated with disability, walking functional capacity and walking speed, particularly in patients with worse disability status of MS (Veldhuijzen van Zanten et al., 2016). From those observations, future research should focus on physical activity and efficient methods of adherence in physical practice for people with MS. Our results also highlight the importance of strength training to improve muscles functions, specifically the strengthening of KF muscle early in programs delineated to MS patients, since the disease diagnosis. We also emphasize possible significance of balance training, which contributes to a better sensory integration among the proprioception, visual and vestibular systems.

We conducted this study evaluating the percentage change in distance walked in the 6MWT and its physiological correlates e possible predictors based on muscle strength and postural control in women with mild MS, but there are some limitations. These include no performed kinematic analysis to verify the influence of knee strength during the gait; the sample comprised only women with mild RRMS; different types of medications taking by the patients.

5. Conclusions

Findings of the present study indicated that women with mild MS presented decline in walking distance over the 6MWT, low knee flexor muscle strength and impaired integration in the sensory systems involved in balance, compared to women without MS.

Finally, the knee flexor strength explained differences between groups in walking. In addition, the knee flexor strength and balance, in the most challenged task (foam with eyes closed), presented as predictors of walking slowing down in the 6MWT, and may explain walking related motor fatigability during prolonged walking in patients with mild MS.

These results highlight the importance of interventions for reducing the decline in prolonged walking performance in women with mild MS, and our data suggest that this might be accomplished through exercise training programs that target lower extremity muscle strength, particularly the knee flexors, and balance exercises with altered sensory conditions.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of interest

Declarations of interest: none.

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Multiple Sclerosis and Related Disorders 30 (2019) 208–214

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Validation of the Brazilian version of the patient-determined disease steps scale in persons with multiple sclerosis

Ana C. de David[a,*], Jeffer E. Sasaki[b], Cintia Ramari[a], Carlos B. Tauil[c], Andrea G. Moraes[a], Flávia Martins[d], Felipe von Glehn[e], Robert W. Motl[f]

[a] Laboratory of Human Motion Analysis, Faculty of Physical Education, University of Brasilia, Via L4 Norte – Campus Darcy Ribeiro, Brasília, DF, Brazil
[b] Department of Sport Sciences, Federal University of Triangulo Mineiro, Uberaba, MG, Brazil
[c] Department of Medical Sciences, University of Brasília, DF, Brazil
[d] Department of Neurology, Brasilia District Hospital, Brasília, DF, Brazil
[e] Department of Neuroimmunology, University of Campinas, SP, Brazil
[f] Department of Physical Therapy, University of Alabama at Birmingham, Birmingham, AL, USA

ARTICLE INFO

Keywords:
Disability
Multiple sclerosis
PDDS scale
Brazilian version

ABSTRACT

Objective: The present study translated and adapted the Brazilian version of the Patient-Determined Disease Steps (PDDS) scale and tested its validity and reproducibility in Brazilian persons with multiple sclerosis (MS).
Methods: The PDDS underwent translation and back-translation procedures for producing a Brazilian Portuguese version of the PDDS (PDDS/BR). Sixty-three patients with MS (48 females) completed the PDDS/BR and underwent a neurological examination for generation of Expanded Disability Status Scale (EDSS) scores. Participants further performed the following tests: Timed 25-Foot Walk (T25FW), Timed Up and Go (TUG), six-minute walk test (6MWT), Nine Hole Peg (9HPT), and Symbol Digit Modalities Test (SDMT). Construct validity of PDDS/BR scores was determined by Spearman correlation with EDSS, and comparison of correlations between PDDS/BR and EDSS with the functional tests. We examined overall correct classification of disability categories (i.e., mild, moderate, or severe disability) by the PDDS/BR in relation to the EDSS. Test-retest reproducibility of PDDS/BR scores was examined in a subsample of 31 participants after 15 days.
Results: There was a strong relationship between the PDDS/BR and EDSS scores ($\rho = 0.723$, $p < 0.05$). The correlations with TUG, T25FW, 6MWT, and 9HPT were comparable for the PDDS/BR and EDSS scores. Overall correct classification of disability categories by the PDDS/BR was 79.3%. Results indicated excellent test-retest reproducibility for the PDDS/BR (Intraclass Correlation Coefficient = 0.911, 95% CI: 0.685–0.918).
Conclusion: The PDDS/BR scores provide a valid and reliable assessment of mobility disability and may be used by researchers and neurologists to assess disability status in Brazilians with MS.

1. Introduction

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system that often manifests in disability, with walking impairment representing a common MS feature that compromise the quality of life of those living with the disease (Larocca, 2011). The typical method for assessing disability in MS involves a neurological examination for scoring the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). The EDSS has been an instrumental method for classifying disability status in MS; however, it is a time-consuming clinical assessment administered only by neurologists (Learmonth et al., 2013).

The Patient-Determined Disease Scale (PDDS), which is a patient-reported measure of mobility disability (Learmonth et al., 2013), represents a more feasible instrument for initial screening and/or stratification of disability status in people with MS. The PDDS was developed by researchers associated with the Patient Registry of the North American Research Committee on MS (NARCOMS) and adapted from the physician administered Disease Steps (Hohol et al., 1995) to be a surrogate of the EDSS. The PDDS has nine ordinal levels ranging between 0 (normal) and 8 (Bedridden) and PDDS scores can be converted into classifications of mild, moderate, or severe disability (Learmonth et al., 2013).

To the best of our knowledge, the PDDS has only been validated in three languages (i.e., English, Italian, and Spanish) (Learmonth et al., 2013; Lavorgna et al., 2017; Solà-Valls et al., 2018). One study (Learmonth et al., 2013) examined the validity of the English version of

* Corresponding author.
E-mail addresses: acdavid@unb.br (A.C. de David), jeffer.sasaki@uftm.edu.br (J.E. Sasaki), robmotl@uab.edu (R.W. Motl).

https://doi.org/10.1016/j.msard.2019.02.022
Received 13 November 2018; Received in revised form 19 February 2019; Accepted 21 February 2019

the PDDS in 96 persons with MS. The authors reported strong correlations between EDSS and PDDS scores (ρ = 0.783). In addition, similar correlations were found for the PDDS and EDSS scores with different functional and ambulatory outcomes (Learmonth et al., 2013). Another study adapted and validated an Italian version of the PDDS for measuring disability in a sample of 96 persons with MS (Lavorgna et al., 2017). The relationship between the Italian versions of the EDSS and PDDS was high (ρ = 0.711, R^2 = 0.59), and both instruments presented similar correlations with demographic outcomes, 6-min walk test (6MWT), timed-25 foot walk (T25FW), Timed Up and Go (TUG), 9-Hole Peg Test (9HPT), and Symbol Digit Modalities Test (SDMT).

To date, this instrument has not been translated and validated in Portuguese for applications among Brazilians with MS. This is important for providing health professionals and researchers in Brazil with a disability assessment tool that can be conveniently used to classify the degree of disability in people with MS. The present study translated the PDDS for the Brazilian Portuguese language (PDDS/BR) and tested its validity and reproducibility in a group of Brazilian persons with MS. Based on the methods and results of previous research (Learmonth et al., 2013; Lavorgna et al., 2017), we hypothesized that PDDS/BR scores would present convergent validity with demographic characteristics (i.e., age, disease duration, and body mass index [BMI]), common measures of disability (EDSS, 6MWT), walking speed (T25FW), balance and mobility (TUG), finger dexterity (9HPT). Regarding cognitive impairment (SDMT), we hypothesized that the correlation will be stronger with EDSS than with PDDS/BR scores, as the former emphasizes cognitive assessment substantially more than the latter. We further examined the test-retest reproducibility based on two measures of the PDDS/BR separated by 15 days.

2. Methods

2.1. Translation and adaptation of the PDDS

For translation and adaptation of the PDDS (Learmonth et al., 2013) (see PDDS english version in Appendix A), three proficient translators with experience in health terminology produced three independent forward translations. Problematic items were re-translated into Portuguese version and a consensus version was produced. Some terms in English that did not have a direct translation or are not usual terms in Portuguese (e.g., attack, 25 feet, cane or single crutch, and scooter) needed to be discussed for identifying the most accurate translation. Subsequently, the Portuguese version was back translated into English and compared to the original one. The consensus translation was evaluated in terms of simplicity, correctness of language and equivalence to the original version by three neurologists with experience in MS and a bilingual (English-Portuguese) professional (see final PDDS/BR version in Appendix B).

2.2. Participants

MS patients from the Neurology Sector of the Base Hospital Institute (Brasília, Brazil) were enrolled in this study between March and May 2018. A fixed sample size was not set for stopping study enrollment. Therefore, we enrolled the maximum number of participants as we could during the 3-month period. Inclusion criteria were a confirmed MS diagnosis according to the revised McDonald criteria (Polman et al., 2011), age >18 years, ambulatory with or without an assistive device, and willingness to voluntarily complete testing. We excluded those who had an exacerbation in the past 90 days, an additional neurological disease, or one or more concomitant comorbidities. Ethical approval for this study was obtained from the institutional ethical committee (CAEE: 67098217.5.0000.5553) of the University of Brasilia. Signed informed consent was obtained from each patient prior to enrollment in the study according to the Declaration of Helsinki.

2.3. Demographic, anthropometric, and clinical data

Self-reported data were obtained for age (years), sex (male or female), disease course (primary progressive, secondary progressive, relapsing-remitting, or clinically isolated), and disease duration (years since diagnosis). Height and weight were measured by a trained researcher using a weight scale and a stadiometer. Body mass index (BMI) was calculated according to the Quetelet's index.

2.4. Expanded disability status scale (EDSS)

Participants underwent a neurological examination to obtain EDSS scores (Kurtzke, 1983) by a neurologist responsible for the MS outpatient clinic at the hospital. The neurologist had extensive experience with MS and EDSS application (>15 years). In the current study, the EDSS was considered the criterion method for assessing disability status.

2.5. Patient-Determined disease steps – Brazilian Portuguese version (PDDS/BR)

On the same occasion of the EDSS assessment, participants completed the final version of the PDDS/BR containing nine ordinal levels ranging between 0 (normal) and 8 (Bedridden). They were asked to mark a single option that best represented their disability status. A second administration of the PDDS/BR was made for a subsample of 31 participants after 15 days of the first application. The two scores from the subsample were used to estimate reproducibility of the PDDS/BR.

2.6. Physical function and cognitive testing

Participants also performed a series of tests for mobility, upper body, and cognitive functions. The researcher in charge of conducting these tests was blinded in regards to participants' EDSS and PDDS/BR scores. All tests took place at the same hospital setting and were applied by the same research team using standardized instructions. These tests are described next.

2.6.1. Timed 25-foot walk (T25FW)

The T25FW was used as an objective measure of walking speed (Kaufman et al., 2000). A straight-line 25-foot course was marked on the floor and participants were instructed to stand behind the starting line and to walk as quickly and safely as possible to the other end. They were asked not to slow down until taking some steps past the end mark. Participants completed two trials of the T25FW and a researcher timed the trials with a stopwatch while walking along side the participants. The T25FW score was the average of the two trials in seconds.

2.6.2. Timed up and go (TUG)

The TUG was used to objectively assess functional mobility (Sebastião et al., 2016). The course for this test was set up according to standardized descriptions (Sebastião et al., 2016). Basically, a chair was positioned against a wall and a cone placed 3 m away from the chair. Participants were instructed to perform the test as quickly and safely as possible by standing up (without using their hands), walking towards and around the cone, and walking back to sit down again. Participants were allowed to use assistive devices to walk if needed. Each participant completed three trials and the final score was computed as the average time (in seconds) from the three trials.

2.6.3. Six minute walk test (6MWT)

The 6MWT was administered as a measure of lower body endurance (Enright, 2003; Goldman et al., 2008). Participants were instructed to walk as fast and far as possible around a 10-m course during a period of 6 min (Enright, 2003; Goldman et al., 2008). Participants were allowed to slow down or to stop momentarily, if necessary, during the test. The

outcome for the test was the total distance walked in meters.

2.6.4. Nine hole peg test (9HPT)

On this test, the board was placed in front of the participants, with the peg container in front of the hand being tested and the side with the peg holes in front of the other hand (Goodkin et al., 1988). Participants were instructed to pick up the pegs one at a time, using only one hand, and to place them into the holes as quickly as possible in any order they wished (Goodkin et al., 1988). After filling all nine holes, participants removed the pegs one at a time and placed them back in the container as quickly as they could (Goodkin et al., 1988). Each participant performed two trials with the dominant hand (9HPT Dom.) and two with the non-dominant hand (9HPT Non-dom.). A researcher timed the trials with a stopwatch. The average of the two trials was considered the final score for each hand.

2.6.5. Symbol digit modalities test (SDMT)

The SDMT was administered as a measure of cognitive function (Benedict et al., 2017). Participants were given the SDMT testing sheet and were instructed to use a reference key to pair symbols with their corresponding numbers. They were asked to call the numbers out loud as quickly as they could during a period of 90 s (Benedict et al., 2017). A researcher scored the answers and kept track of the time. The score was the final number of correct answers.

2.7. Statistical analysis

Median, first and third quartile (Q1–Q3) were computed for all variables and utilized to characterize the sample. The Shapiro–Wilk test was used to check whether data were normally distributed or not. The results indicated non-normal distribution of data for both the PDDS/BR and EDSS scores. Therefore, the relationship between PDDS/BR and EDSS was examined with a Spearman rho rank order correlation *(ρ)* and a scatter plot for visual inspection of data dispersion. For checking the agreement of disability status classification (i.e., mild, moderate, and severe disability) by PDDS/BR and EDDS cut-points, we used the *kappa* agreement test. Construct convergent validity of the PDDS/BR in relation to the EDSS was determined by examining Spearman rho rank order correlation coefficients with demographic characteristics, 6MWT, T25FW, TUG, 9HPT, and with the SDMT. Correlation coefficients of <0.3, ≥ 0.3 to <0.5, ≥ 0.5 to <0.7, and ≥ 0.7 were interpreted as very weak, weak, moderate, and strong respectively (Mukaka, 2012). The Fisher's *z*-test was used to compare the Spearman correlation coefficients of the two scales (EDSS and PDDS/BR) with all the other variables. For test-retest reproducibility of the PDDS/BR, the intraclass correlation coefficient (ICC) was calculated to examine the degree of reproducibility between the two measures taken 15 days apart. A p value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS package.

3. Results

3.1. Sample characteristics

Of the 120 individuals who were invited, sixty-three (48F and 15 M; 62 relapsing-remitting MS and 1 primary progressive MS) took part in the study. Of the 63 participants, five did not complete the functional tests due to fatigue. Thus, complete data were obtained for 58 participants. Participant characteristics and scores from the different assessments are presented in Table 1. The median EDSS score indicated a mild level of disability for the sample overall, and the entire range of scores was between 0 and 7, indicating that the sample included persons with mild through severe disability status. However, most participants were mildly or moderately disabled, as indicated by the median value and interquartile range.

Table 1
Participant characteristics (n = 58).

	Median (Interquartile range)
Age (years)	37.0 (18.0–69.0)
BMI (kg/m^2)	24.4 (22.3–29.2)
Disease duration (years)	7.0 (4.0–11.0)
EDSS	2.5 (1.0–4.5)
PDDS/BR	1.0 (0.0–3.0)
9HPT Dominant (s)	22.0 (13.5–75.5)
9HPT Non-dominant (s)	23.8 (15.6–57.0)
TUG (s)	9.4 (7.4–12.5)
T25FW (s)	5.5 (4.5–8.0)
6MWT (m)	350.0 (230.0–440.0)
SDMT	39.0 (31.5–50.0)

BMI - body mass index; EDSS - expanded disability status scale; PDDS/BR – Brazilian Portuguese version of the patient-determined disease steps; 9HPT – nine hole peg test; TUG – timed up and go; T25FW – timed 25-foot walk; 6MWT – 6-min walk test; SDMT: symbol digit modalities test.

3.2. Criterion validity of the PDDS/BR

The scores obtained with the PDDS/BR version demonstrated strong relationship with scores from the criterion method EDSS ($\rho = 0.723$, $p < 0.05$). The scatter plot of scores between PDDS/BR and EDDS is provided in Fig. 1. The results indicate that the relationship was strong but not linear and, although the scores were not aligned point-by-point, it is possible to observe some level of misreporting of disability level with the PDDS/BR, as there was considerable variability in EDSS values for each PDDS/BR score.

For classifying individuals into categories of mild, moderate, and severe disability, the agreement between EDSS (criterion method) and PDDS/BR was moderate ($k = 0.58$, $p < 0.001$). Table 2 displays the classification matrix, where the central diagonal line indicates those people with MS classified similarly according to both methods. In 46 of 58 cases, the classification was the same based on the matrix. The overall percent correct classification of disability status by the PDDS/BR was 79.3% in relation to EDSS. Percent correct classification by the PDDS/BR for mild, moderate, and severe disability was 89%, 55%, and 64%, respectively. Of note, the PDDS/BR presented a greater tendency to underestimate disability status (values to the left of diagonal line) compared to the EDSS.

3.3. Construct convergent validity

The bivariate correlations in Table 3 indicated strong and comparable associations between the PDDS/BR and EDSS scores with TUG, T25FW, and 6MWT. There further were strong and comparable associations between the PDDS/BR and EDSS with 9HPT for both dominant and non-dominant hands. None of the correlation coefficients were significantly different between EDSS and PDDS/BR scores. This pattern of correlations supports the construct convergent validity of the PDDS/BR as a measure of physical function, and this is comparable with previous research (Learmonth et al., 2013; Lavorgna et al., 2017) and the results with the EDSS. There was a moderate correlation between EDSS scores and SDMT, but no significant correlation of the latter with PDDS/BR scores. The correlations of EDSS and PDDS/BR scores with age, BMI, and disease duration were mostly weak and non-significant. The latter pattern of correlations supports that the PDDS/BR does not reflect demographic, morphologic, and clinical characteristics of MS; this is comparable with previous research (Learmonth et al., 2013; Lavorgna et al., 2017) and with the results seen for the EDSS.

3.4. Test-retest reproducibility

The test-retest reproducibility of PDDS/BR scores was examined in a subsample of 31 persons with MS. Fig. 2 displays the scatter plot between PDDS/BR test and retest scores. Additional analyses indicated

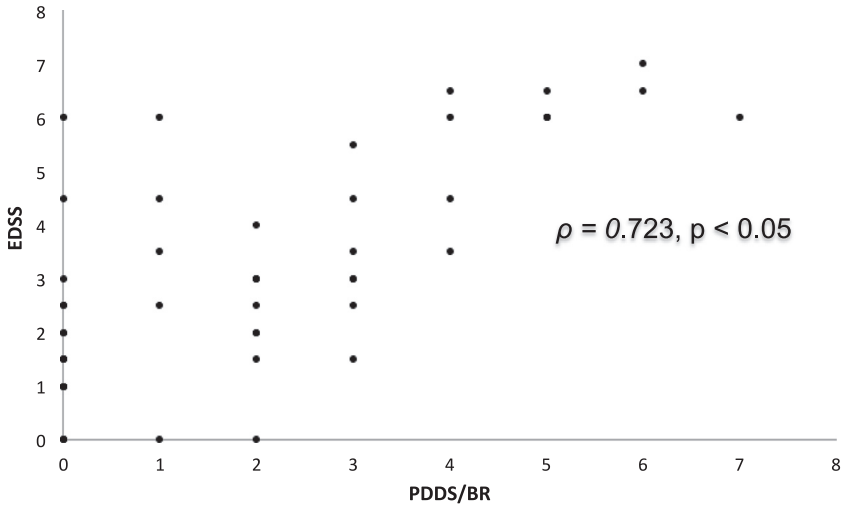

Fig. 1. Scatter plot of EDSS and PDDS/BR scores.

excellent test-retest reproducibility for the PDDS/BR, with high scores for intraclass correlation coefficient (ICC = 0.911, 95% IC: 0.685–0.918) and Cronbach's Alpha (α = 0.916).

4. Discussion

The purpose of the current study was to validate scores from the PDDS/BR in persons with MS. The results indicated that PDDS/BR scores provide a valid and reliable measure of neurological disability, particularly mobility disability, and may be used as an alternative instrument to the EDSS in research (e.g., clinical and epidemiological) and by neurologists, especially when the main objective is an overall classification of disability status for stratification in research. For example, in surveys or remote research, it is not always feasible to use the EDSS to assess disability status. In such cases, the PDDS has been used to provide a valid patient-reported classification of disability in people with MS (Sasaki et al., 2018; Hubbard et al., 2015; Marrie et al., 2005; Wicks et al., 2012).

Previous studies have validated the PDDS in English (Learmonth et al., 2013), Italian (Lavorgna et al., 2017), and Spanish (Solà-Valls et al., 2018) languages for utilization in MS. The Spanish version was validated as a telephone-based instrument (Solà-Valls et al., 2018), whereas the other two versions were validated as paper-based instruments (Learmonth et al., 2013; Lavorgna et al., 2017). These studies presented strong correlations between the PDDS and EDSS (ρ = 0.783 (Learmonth et al., 2013), ρ = 0.711 (Lavorgna et al., 2017), ρ = 0.88 (Solà-Valls et al., 2018)), as also observed in the current study (ρ = 0.723). Importantly, these studies did not demonstrate a one-to-one relation between EDSS and PDDS, which corroborates our results. A PDDS of 1 generally corresponds to an EDSS that is slightly higher. The results from the studies by Learmonth et al. (2013) and Lavorgna et al. (2017) also support the misreporting of disability level with the PDDS/BR observed for some cases in our study. Nevertheless, some level of response bias is always present in self-report instruments and, thus, researchers and/or clinicians should be aware of it when using the PDDS/BR.

Table 3
Bivariate Spearman correlations of the EDSS and PDDS/BR with different variables.

	EDSS	PDDS/BR	*p*
Age	0.27 (0.02, 0.48)	0.25 (−0.02, 0.48)	0.407
BMI	0.12 (−0.12, 0.38)	0.17 (−0.07, 0.40)	0.479
Disease Duration	0.03 (−0.25, 0.29)	−0.05 (−0.33, 0.20)	0.312
9HPT Dom.	0.60 (0.39, 0.74)	0.45 (0.24, 0.62)	0.227
9HPT Non-Dom.	0.64 (0.46, 0.76)	0.50 (0.26, 0.69)	0.219
TUG	0.82 (0.72, 0.89)	0.76 (0.62, 0.87)	0.446
T25FW	0.77 (0.60, 0.86)	0.72 (0.54, 0.84)	0.375
6MWT	−0.79 (−0.88, −0.65)	−0.74 (−0.84, −0.56)	0.215
SDMT	−0.42 (−0.61, −0.15)	−0.114 (−0.40, 0.18)	0.095

p-value was derived from Fisher's Z test to test for differences between correlations of EDSS and PDDS/BR with the other variables.
BMI - body mass index; EDSS - expanded disability status scale; PDDS/BR – Brazilian Portuguese version of the patient-determined disease steps; 9HPT – nine hole peg test; TUG – timed up and go; T25FW – timed 25-foot walk; 6MWT – 6-min walk test; SDMT: symbol digit modalities test.

In our study, we also observed similar side-by-side associations of the EDSS and PDDS/BR with demographic, clinical, functional, and ambulatory scores. Of note, our results demonstrated that the PDDS/BR exhibited the strongest correlations with ambulatory scores, denoting the focus of the instrument in assessing gait impairment as a major determinant of disability status in MS. Similar patterns of correlations between the PDDS and ambulatory outcomes were observed in the studies by Learmonth et al. (2013) and Lavorgna et al. (2017), with the latter exhibiting weaker correlations. In the study by Learmonth et al. (2013), the correlations between PDDS and 6MWT, TUG, and T25FW were ρ = −0.704, ρ = 0.717, and ρ = 0.627; in the study by Lavorgna et al. (2017), the correlations were ρ = −0.633,

Table 2
Disability Categorization according to EDSS and PDDS/BR scores.

EDSS CATEGORIES	PDDS/BR CATEGORIES			
	Mild disability (0–2)	Moderate disability (3–4)	Severe disability (≥5)	Total
Mild disability(0–3)	34	4	0	38
Moderate disability(3.5–5.5)	4	5	0	9
Severe disability(≥6)	2	2	7	11
Total	40	11	7	58

Note: These EDSS and PDDS cut-points for disability categories are commonly used in research (Sasaki et al., 2018; Gray et al. 2009, Reider et al., 2017).

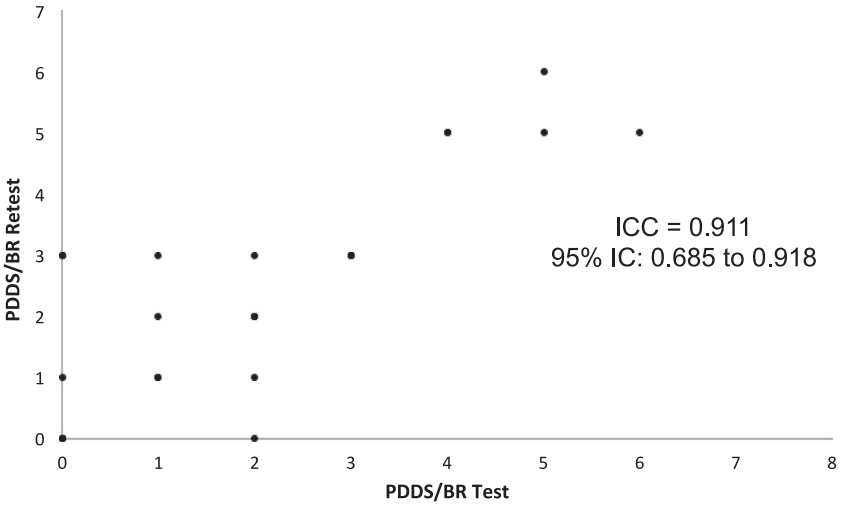

Fig. 2. PDDS/BR test and retest scores in the current study.

$\rho = 0.479$, and $\rho = 0.587$, respectively.

In line with Lavorgna et al. (2017), our results indicated only a moderate correlation between PDDS/BR and 9HPT scores. This is not surprising, as decrements in upper body function may not necessarily accompany decrements in lower body function. Studies have suggested that the loss of strength vary in lower and upper extremity muscles, even though a parallel decline occurs with aging (Izquierdo et al., 1999).

Regarding the relationship between PDDS/BR and cognitive function, we observed no significant association between the PDDS/BR and SDMT score in the current study; which is the opposite of Learmonth et al. (2013) and Lavorgna et al. (2017)), who reported significant moderate correlations between the two scales. This discrepancy may be due to the overall low scores for PDDS/BR in our study. Therefore, one reason we did not observe a significant correlation for the PDDS/BR and SDMT score was likely the small number of participants with significant cognitive impairment. On the other hand, the EDSS did demonstrate a significant correlation with the SDMT. However, the EDSS includes Functional Systems Scores (FSS), where one of the functions tested is the mental one. The PDDS/BR is mostly focused on mobility disability and, thus, may only detect cognitive impairment when it occurs concomitantly with mobility decrements. In samples with a substantial spread of PDDS scores, it is likely that such cases will occur, as was probably the case for the studies by Learmonth et al. (2013) and Lavorgna et al. (2017). Therefore, researchers and clinicians should be aware that additional assessments other than the PDDS-BR are necessary if the goal is to assess cognitive impairment.

An important result from our study was the classification accuracy of disability status categories by the PDDS/BR in relation to the EDSS. The overall correct classification was 79.3%, denoting a high classification agreement, even though when considering chance alone (*kappa* agreement) the agreement decays to a moderate one. It is important to note that the classifications by the PDDS/BR tended to slightly underestimate the disability status compared to the EDSS. Disability status classification is of major interest because researchers and clinicians are often concerned in stratifying individuals as those having mild, moderate, or severe disability. The results thus suggest that the PDDS/BR may be used for such purpose in research as well as in the clinical practice.

In this study, the PDDS/BR further demonstrated excellent test-retest reproducibility, as denoted by the high ICC score. This suggests that, when used on two different occasions separated by a short period of time, the self-reporting of disability level in the PDDS/BR by people with MS is likely to be the same. However, this result should be interpreted with caution, as some participants considerably misreported their disability status (i.e., 2–3 points off) between the two timepoints. It is possible that the ICC in a more homogeneous sample could in fact be lower, but this would need to be tested in different samples. Another fact that will need to be tested in future is the sensitivity of the PDDS/BR in assessing changes in disability status over time; but this was beyond the scope of the current study.

This study has limitations. The sample was relatively small and, thus, the spread of scores was limited. The validity of the PDDS/BR for higher disability levels will need to be further examined in larger samples. Another limitation was the lack of participants with different disease courses other than relapsing-remitting. Progressive forms of MS affect function more constantly. Thus, self-reporting of disability in these cases may differ compared to relapsing-remitting MS. Finally, the lack of a free-living physical activity measure prevented us to examine the relationship between PDDS/BR and functionality in real world settings. Future studies could use an objective measure of physical activity, such accelerometry, to evaluate this association.

5. Conclusions

We validated the Brazilian version of the Patient-Determined Disease Steps (PDDS/BR) in people with MS. The correlations indicated strong and comparable associations between the PDDS/BR and EDSS with TUG, T25FW, and 6MWT. There further were strong and comparable associations between the PDDS/BR and EDSS with 9HPT for both dominant and non-dominant hands. That pattern of associations supports the convergent validity of the PDDS/BR as a measure of mobility disability in MS. In addition, PDDS/BR classification accuracy regarding disability status categories was high, demonstrating that it can be a useful instrument for general stratification of persons with MS for research and clinical purposes. Taken together, the results indicated that PDDS/BR scores provide a valid and reliable assessment application in clinical and epidemiological research and may be used as an alternative instrument for the EDSS.

Funding

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - finance code 001.

Declarations of interest

None.

Acknowledgements

The authors would like to acknowledge Professor Lauro C. Vianna, PhD from University of Brasília and Professor Emerson Sebastião, PhD from the Northern University of Illinois for their collaboration in the translation and back-translation of the PDDS instrument.

Appendix A. PDDS English version

Patient-determined disease steps

Please read the choices listed below and choose the one that best describes your own situation. This scale focuses mainly on how well you walk. Not everyone will find a description that reflects their condition exactly, but please mark the one category that describes your situation the closest.

1 **Normal:** I may have some mild symptoms, mostly sensory due to MS but they do not limit my activity. If I do have an attack, I return to normal when the attack has passed.
2 **Mild disability:** I have some noticeable symptoms from my MS but they are minor and have only a small effect on my lifestyle.
3 **Moderate disability:** I don't have any limitations in my walking ability. However, I do have significant problems due to MS that limit daily activities in other ways.
4 **Gait disability:** MS does interfere with my activities, especially my walking. I can work a full day, but athletic or physically demanding activities are more difficult than they used to be. I usually don't need a cane or other assistance to walk, but I might need some assistance during an attack.
5 **Early cane:** I use a cane or a single crutch or some other form of support (such as touching a wall or leaning on someone's arm) for walking all the time or part of the time, especially when walking outside. I think I can walk 25 feet in 20 s without a cane or crutch. I always need some assistance (cane or crutch) if I want to walk as far as 3 blocks.
6 **Late cane:** To be able to walk 25 feet, I have to have a cane, crutch or someone to hold onto. I can get around the house or other buildings by holding onto furniture or touching the walls for support. I may use a scooter or wheelchair if I want to go greater distances.
7 **Bilateral support:** To be able to walk as far as 25 feet I must have 2 canes or crutches or a walker. I may use a scooter or wheelchair for longer distances.
8 **Wheelchair/Scooter:** My main form of mobility is a wheelchair. I may be able to stand and/or take one or two steps, but I can't walk 25 feet, even with crutches or a walker.
9 **Bedridden:** Unable to sit in a wheelchair for more than one hour.

Appendix B. PDDS Brazilian version

Graus da Doença Determinados pelo Paciente

Por favor, leia as opções listadas abaixo e escolha uma que melhor descreva a sua situação. Essa escala foca principalmente na sua capacidade de caminhar. Nem todos acharão uma descrição que reflita exatamente sua condição, mas, por favor, marque uma categoria que descreva o mais próximo de sua situação.

1 **Normal**: Eu posso ter alguns sintomas sensoriais leves, devido à esclerose múltipla, mas eles não limitam minhas atividades. Se eu tenho um surto, eu retorno ao normal depois que ele passa.
2 **Incapacidade Leve**: Eu apresento alguns sintomas visíveis relacionados à esclerose múltipla, mas eles são leves e possuem apenas um pequeno efeito no meu estilo de vida.
3 **Incapacidade Moderada**: Eu não tenho quaisquer limitações na minha habilidade de andar. No entanto, eu tenho problemas significativos devido à esclerose múltipla que limitam minhas atividades diárias em outros aspectos.
4 **Incapacidade no caminhar**: A esclerose múltipla interfere em minhas atividades, especialmente no meu caminhar. Eu posso trabalhar um dia inteiro, mas atividades atléticas ou fisicamente exigentes são mais difíceis do que costumavam ser. Geralmente, eu não preciso de uma bengala ou outro auxílio para andar, mas eu posso precisar de alguma assistência durante um surto.
5 **Bengala Precoce**: Eu uso bengala ou uma muleta ou alguma outra forma de suporte (tal como me apoiar em uma parede ou no braço de alguém) durante todo o tempo, ou parte do tempo, especialmente quando caminho ao ar livre. Acho que posso andar aproximadamente 8 metros em 20 segundos sem uma bengala ou muleta. Eu sempre preciso de alguma assistência (bengala ou muleta) se eu quero andar mais do que três quarteirões.
6 **Bengala Tardia**: Para ser capaz de caminhar aproximadamente 8 metros, eu tenho que ter uma bengala, muleta ou me apoiar em alguém. Eu posso andar pela casa ou por outros prédios segurando nos móveis ou me apoiando nas paredes. Posso usar uma scooter ou uma cadeira de rodas se eu quero percorrer distâncias maiores.
7 **Apoio Bilateral**: Para ser capaz de caminhar mais de 8 metros eu necessito de duas bengalas, duas muletas ou um andador. Eu posso usar uma scooter ou cadeira de rodas para distâncias maiores.
8 **Cadeira de Rodas/Scooter**: Minha principal forma de mobilidade é uma cadeira de rodas. Eu consigo ficar de pé e/ou dar um ou dois passos, porém não consigo andar aproximadamente 8 metros, mesmo com muletas ou um andador.
9 **Acamado**: Sou incapaz de permanecer sentado em uma cadeira de rodas por mais de uma hora.

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Expert Review of Neurotherapeutics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iern20

Clinical assessment, management, and rehabilitation of walking impairment in MS: an expert review

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To cite this article: Bernardita Soler , Cintia Ramari , Maxime Valet , Ulrik Dalgas & Peter Feys (2020): Clinical assessment, management, and rehabilitation of walking impairment in MS: an expert review, Expert Review of Neurotherapeutics, DOI: 10.1080/14737175.2020.1801425

To link to this article: https://doi.org/10.1080/14737175.2020.1801425

Accepted author version posted online: 30 Jul 2020.
Published online: 09 Aug 2020.

EXPERT REVIEW OF NEUROTHERAPEUTICS
https://doi.org/10.1080/14737175.2020.1801425

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REVIEW

Clinical assessment, management, and rehabilitation of walking impairment in MS: an expert review

Bernardita Soler [a,b], Cintia Ramari[c], Maxime Valet[d,e], Ulrik Dalgas[f] and Peter Feys[g]

[a]Neurology Service, Hospital Doctor Sótero Del Río, Santiago, Chile; [b]Neurology Department, Pontificia Universidad Católica De Chile, Santiago, Chile; [c]Faculty of Physical Education, University of Brasília, Brasília, Brazil; [d]Cliniques universitaires Saint-Luc, Service de Médecine Physique et Réadaptation, Brussels, Belgium; [e]Université catholique de Louvain, Secteur des Sciences de la Santé, Institut de Recherche Expérimentale et Clinique, Neuromusculoskeletal lab (NMSK), Brussels, Belgium; [f]Exercise Biology, Department of Public Health, Aarhus University, Aarhus, Denmark; [g]REVAL, Rehabilitation Research Center, Faculty of Rehabilitation Sciences, Hasselt University, Hasselt, Belgium

ABSTRACT

Introduction: One of the most common and life-altering consequences of Multiple Sclerosis (MS) is walking impairment. The distance, speed, and Gait pattern functions are components of the International Classification of Functioning, Disability, and Health (ICF) and are also predictors of dependency in terms of daily living activities in patients with MS (pwMS).

Areas covered: This article provides an overview of walking impairment in pwMS, with focus on the assessment of gait and the rehabilitation approaches.

Expert opinion: The authors recommend that pwMS undergo gait assessment integrating the ICF perspective using validated clinical outcome measures that cover spatiotemporal gait parameters. Moreover, assessment of walking speed with short walking capacity tests such as the timed 25-foot walk (T25FW) or the 10-m walk test (10 MWT) and tests for walking distance with middle distance tests such as the 2-min walk test (2MWT) and the 6-min walk test (6MWT). This review further highlights strategies that may restore walking function including pharmacological symptomatic treatment and non-pharmacological rehabilitation approaches such as exercise and task-specific training providing an appraisal of mobility targeted therapies to be considered when planning multidisciplinary comprehensive-care of pwMS. Finally, new and novel strategies such as motor imagery and rhythmic auditory stimulation have been developed to improve walking speed and distance in pwMS.

ARTICLE HISTORY
Received 27 May 2020
Accepted 22 July 2020

KEYWORDS
Ambulation; ICF; multiple sclerosis; rehabilitation; walking assessment

1. Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory, neurodegenerative disease that causes demyelination as well as axonal degeneration in the central nervous system (CNS). It is the leading cause of progressive functional impairment in young adults, affecting approximately 2.5 million people worldwide [1,2]. One of the most common and life-altering consequences of MS is walking dysfunction, caused by a variety of impairments including ataxia, muscular weakness, and spasticity. Other factors that contribute to gait dysfunction and thus reduced mobility are cognition, fatigability, and urinary symptoms.

Three of four persons with MS (pwMS) report reduced mobility due to impaired walking function at some point during their lifetime [3,4]. Walking impairment is perceived as the most limiting symptom, affecting the quality of life of patients [4–6]. Indeed, walking performance is included when determining the level of disability in pwMS. For example, the timed 25-foot walk (T25FW) is part of the Multiple Sclerosis Functional Walking Composite (MSFC), while walking performance is of major importance in the 4–7 range of the Expanded Disability Status Scale (EDSS) [7]. Walking is affected in up 89% in patients with EDSS score between 4.5 and 5 and 22% in patients with EDSS between 1 and 3.5 [8].

The International classification of functioning, disability, and Health (ICF) developed by the World Health Organization (WHO) conceptualizes the functioning of patients at the levels of body function and structure, activity, and participation, taking into account environmental and personal factors (see Figure 1). The ICF is a tool that allows the classification and the labeling of the different components of walking that are evaluated.

ICF defines walking as 'moving along the surface on foot, step by step, so that one foot is always on the ground, such as when rolling, sauntering, walking forwards, backwards or side-ways.' The distance, speed, and Gait pattern (b770) are predictors of dependency in terms of activities of daily living [8,9]. The ICF proposes that, at the ICF activity, walking can be measured over short distances (d4500) and walking over long distances. We additionally proposed the evaluation of 'middle' distances for the 2- and 6-min walking test [8]. At ICF body function and structure level, gait can be measured with the analyses of temporal and spatial parameters such as cadence and step length, being part of the Gait pattern situated within neuromusculoskeletal and movement-related functions (b770). In this review, we focus on the evaluation of ICF body

CONTACT Peter Feys peter.feys@uhasselt.be Reval Rehabilitation Research Center, Faculty of Rehabilitation Science, Hasselt University, Hasselt 3500, Belgium

Article highlights

- Walking dysfunction is present in the majority of pwMS and contributes to disability and daily living restrictions.
- Walking can be categorized according to ICF, where the gait pattern is categorized at the 'ICF body function level,' whereas walking capacity and perceived walking ability are categorized at 'ICF activity level.'
- The abnormal MS gait pattern can most often be characterized as either paretic or spastic, cerebellar, sensory ataxia, or mixed, which have consequences for the subsequent symptomatic treatment and rehabilitation strategies.
- Research and clinical practice are encouraged to apply validated walking outcomes with well-established MS-specific values of clinically meaningful changes.
- Symptomatic treatment focuses on impairments and can effectively improve walking speed and gait pattern in pwMS, and should, therefore, be included in multi-disciplinary treatment programs.
- Exercise and task-specific training have well-established beneficial effects on walking speed and distance in pwMS.

function and activity level related to walking dysfunction and related impairments, without including physical activity.

Moreover, this article mainly aims to provide an overview of walking impairment in pwMS, focusing on the assessment of gait within the ICF framework. Progress has been made in comprehensive care including management and rehabilitation of symptoms [7]. Therefore, we also highlight strategies that may restore walking function including pharmacologic symptomatic treatment and rehabilitation interventions. We, therefore, provide an appraisal of mobility targeted therapies that may be included in the multidisciplinary and comprehensive care of pwMS.

2. Characteristics of gait patterns

Gait pattern is defined by the ICF as functions of movement patterns associated with walking, running, or other whole-body movements including impairments such as spastic gait, hemiplegic gait, and asymmetric gait.

The gait patterns in MS can be divided into four subgroups (pyramidal or spastic paresis pattern, sensory or unstable gait pattern, cerebellar gait pattern, and mixed gait pattern) and are typified by decreased knee and ankle flexion, reduced dynamic stability, and increased variability of movements [7,10]. Even in pwMS with low disability (EDSS <3.5) gait analysis shows slower walking speed with decreased cadence, shorter and wider steps, an increased variability in time

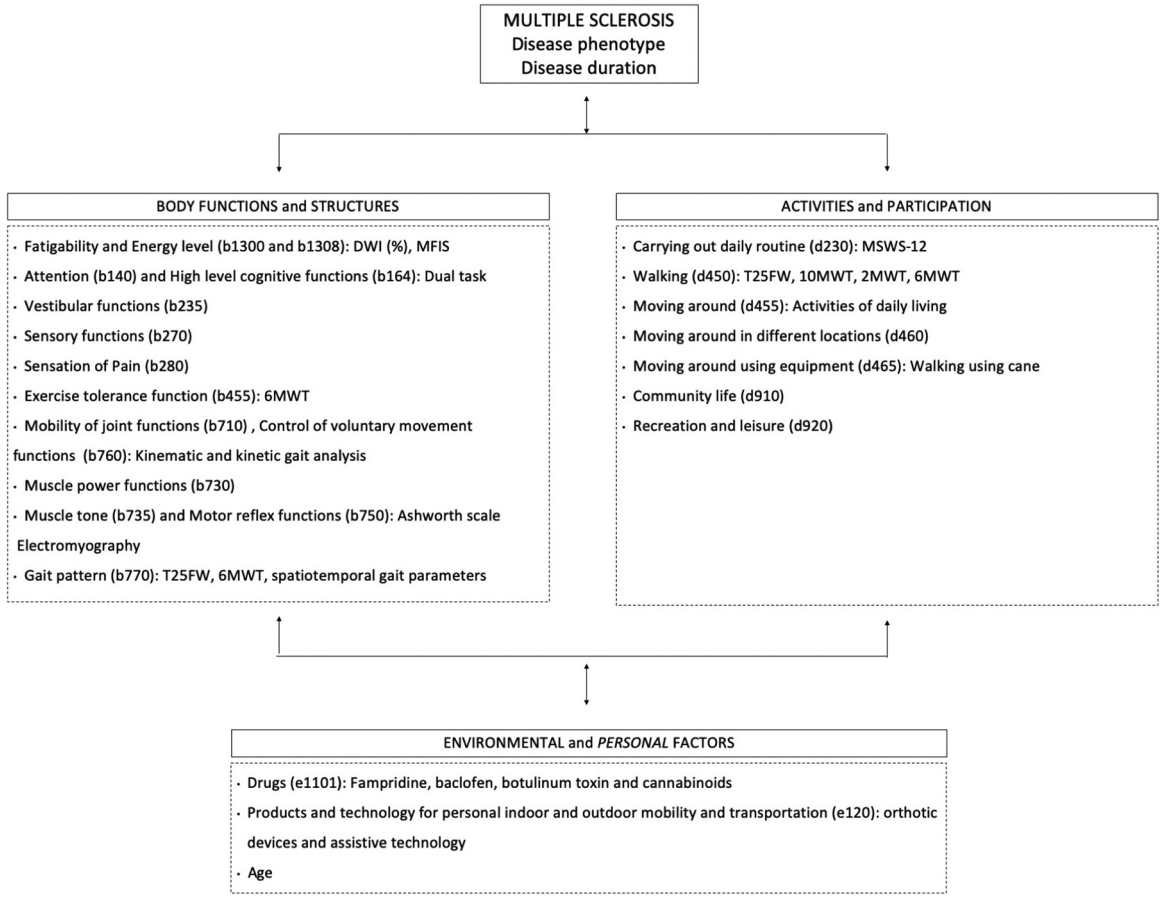

Figure 1. The biopsychosocial perspective of the International Classification of Functioning, Disability and Health (ICF): An overview of the categories from each component (Body functions and structure; Activities and participation; Environmental factors) included in the current work.

T25FWT: 25 timed foot walking test, 10 MWT: 10 m walking test, MSWS-12: 12-Item multiple sclerosis walking scale, 2MWT: 2 min walking test, 6MWT: 6 min walking test, DWI: distance walking index, MFIS: Modified Fatigue Impact scale.

between steps and with longer time spent in double support when compared to controls [7,11].

From all gait parameters, reduced knee range of motion (ROM) is one of the main kinematic features of MS gait having an accuracy of 83% when differentiating gait in pwMS from controls [4]. Furthermore, this kinematic feature is more pronounced in patients with a pyramidal pattern, which were also the patients that demonstrated the most marked deterioration of walking performance in the clinical walking test over 1 year in the Filli et al. study [4].

The most common pattern in MS is asymmetric spastic paraparesis, but all pyramidal patterns can be observed. The ankle-foot paresis is the most common form, with reduced dorsiflexion and/or weak push-off; and fatigability which is defined as increased weakness over time [11]. The kinematic studies showed a pronounced reduction of knee flexion ROM (particularly during swing phase), resulting in increased left-right asymmetry, and also decreased excursions in the ankle joints [4]. The reduced knee ROM is associated with the slower walking speed present in MS and other pathologies.

Cerebellar gait is characterized by ataxia, poor postural control, dysmetria, dysdiadochokinesia and increased variability in stride length as well as wide base of support and stooped trunk position [11]. The kinematic studies showed an increased spatial variability of leg and trunk movements accompanied by increased toe height during mid-swing phase that may serve as a compensatory strategy to prevent tripping or falling.

The sensory ataxia gait is clinically characterized by postural instability, heel strikes, with a higher walking cadence (number of steps per minute) [11]. The kinematic is characterized by increased dynamic instability as evident by a broad-based gait and excessive trunk movements, both in the mediolateral and anteroposterior direction. These patients have increased ROM in their ankle joints, which may be a strategy for the balance control or may reflect deficient ankle stabilization in gait [4].

3. Assessing walking dysfunction

To closely monitor disease progression and changes related to symptomatic treatment and rehabilitation regular assessment of gait is recommended [12]. Such testing includes evaluations of the Gait pattern, kinematics, walking speed and walking distance as further outlined below (see Figure 2).

3.1. Spatiotemporal parameters

Spatiotemporal parameters offer an evaluation of gait pattern with specific equipment for gait analysis with instrumented walkway such as the GaitRite system [13,14], as well as using wearable inertial sensors [15]. The assessment of spatiotemporal gait parameters generates fast and reliable results regarding asymmetries and changes in gait patterns that may not be detected through a clinical walking test [16]. A systematic review and meta-analysis of gait impairment in pwMS reported significant differences between the gait of pwMS and healthy controls (HC) [17]. The walking impairments depend on the level of disability, but across nine studies an average deficit of 22% was reported when compared to HC for walking with fast speed considering spatiotemporal gait parameters [17]. A moderate effect of MS could be observed in stride time and step length, with pwMS displaying longer stride time and reduced step length. The duration of double support was significantly increased, as well as the step width in pwMS, which also represents balance

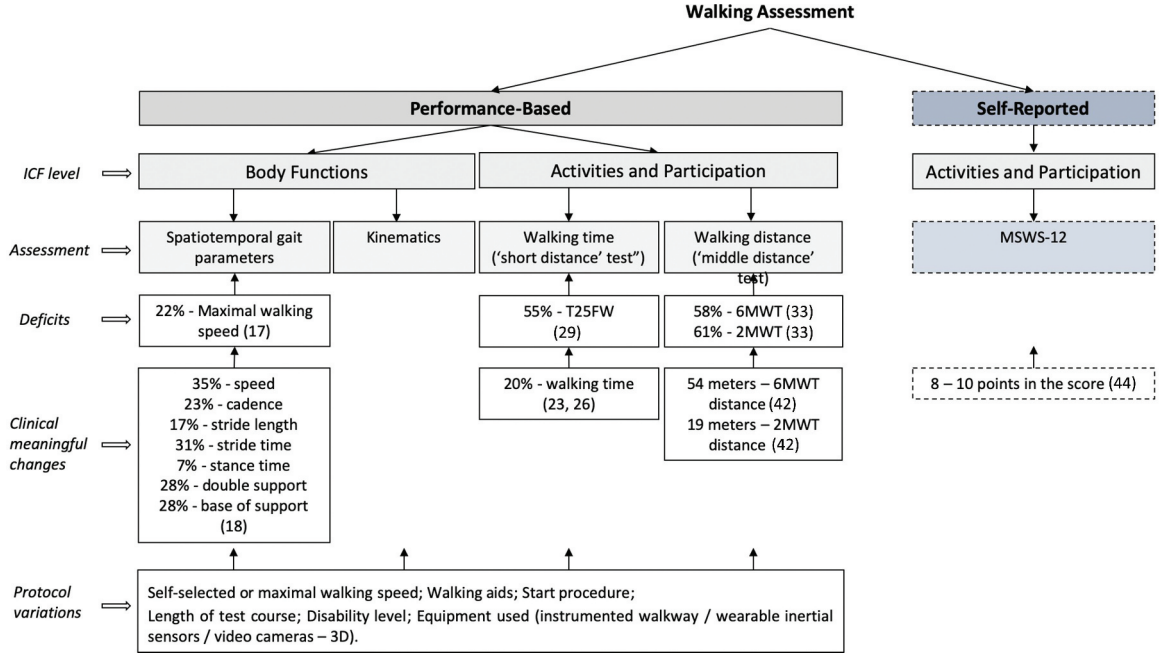

Figure 2. Assessing walking in MS: The assessment of walking recommended, with clinical meaningful change and protocol variants.

25FWT: 25 timed foot walking test, 10 MWT: 10 m walking test, MSWS-12: 12-Item multiple sclerosis walking scale, 2MWT: 2 min walking test, 6MWT: 6 min walking test, DWI: distance walking index, MFIS: Modified Fatigue Impact scale.

control during walking. A shorter time spent in the swing phase as a percentage of the gait cycle and reduced cadence was also detected in MS. In addition, during maximal walking speed condition, the effect of MS on cadence was increased. The same was reported for other gait parameters, in which there is a greater differential effect as the walking speed increases. The study suggests that regardless of the low state of disability of patients (EDSS range: 1.5 to 4.5) reported in the studies, MS has a considerable effect on most of the spatiotemporal parameters, suggesting a gait deficiency in pwMS. To assist interpretation of the reliability and the minimum detectable changes in spatiotemporal gait parameters have been investigated by Decavel et al. [18]. For the T25FW in the fastest speed, the minimum detectable changes for pwMS were the following [for each gait parameter]: 35% [velocity], 23% [cadence], 17% [stride length], 31% [stride time], 7% [stance time], 28% [double support], 38% [base of support].

3.2. Kinematics

To assess additional factors that lead to changes in gait pattern and deficits in ambulation in pwMS, three-dimensional gait analysis (3D), using video cameras in a laboratory environment has been increasingly used in MS research [19]. In addition, in MS kinematics was performed by means of a portable motion analysis system, which consists of small body-worn sensors housing a 3-dimensional gyroscope and triaxial accelerometer [13]. The quantitative measures acquired by a gait analysis system can be used as indicators of the disease progression and to tailor and evaluate the effects of interventions in MS [13,19]. In the Severini et al. study [20], kinematic parameters relating to hip extension, knee flexion, and knee adduction observed during the swing phase were changed in pwMS, which have been associated with lower walking speed and MS disability. In addition, a high variability was found in the kinematics of the ankle joint and peak dorsiflexion during stance. A marked plantar flexion during the swing phase was also found, highlighting the importance of investigating the ankle joint kinematic pattern in MS during walking. This could indicate weakness or lack of voluntary control, but further studies are required to corroborate this hypothesis. Furthermore, greater pelvic tilt was negatively associated with walking speed, and a marked pelvis rotation during the swing phase suggested that pwMS compensate by changes in the hip, knee, and ankle kinematics to promote the advancement of the lower limb [20]. In another study [21], a lower mechanical work was produced at the ankle joint of the more impaired leg compared to the less impaired leg in pwMS suggests a compensatory gait strategy involving reduction in knee flexion and the decrement of knee range of motion during the swing phase which resulted in an increment of lower limb asymmetry and decreased excursion of the ankle joint, leading to the gait deterioration over a period of 1 year [4]. Although the above-mentioned kinematic parameters have been shown as the most prominent findings related to ambulation deficits in MS, kinematic values to define clinical meaningful changes are still to be defined for pwMS.

3.3. Walking short distance

In MS clinical practice, the assessment of walking speed has frequently been done by short walking capacity tests such as the timed 25-foot walk (T25FW) and the 10-m walk test (10MWT) [22]. The T25FW is a component of the MSFC and represents the most well-characterized direct measure of specific walking disability [12], and has been selected as a primary outcome for trials concerning rehabilitation interventions, exercise training, and pharmacological treatments. Short walking tests represent an ideal assessment of walking speed, being easy to administer to a wide range of patients, reliable and valid [23]. From a static start, patients must walk a 25-foot /7.62-meters course as fast as possible, which may resemble relevant daily life situations [24,25].

As a marker of gait function and its relation with functional and health indicators, the T25FW performance can be used to define ecologically valid benchmarks [18,26]. Patients who complete the T25FW in between 6 and 7.99 s are more likely to be unemployed, walking using a cane, require assistance with instrumental activities at daily living and had reduced community ambulation as measured by accelerometer [26]. PwMS who complete the T25FW in 8 or more seconds are associated with unemployment, government health-care assistance, divorce, walking with walkers and in 70% people are unable to perform instrumental activities at daily living.

Walking speed reserve, which is the increase from a preferred walking speed to maximal walking speed, reflects the capacity (what the person can do in an idealized environment) to increase speed in response to different environmental demands. Low walking speed reserve represents the incapacity of increasing walking speed, suggesting that the individual typically walks at, or close to, their maximal speed [27]. Gijbels et al. [24] investigated the characteristics of short walking tests and the impact of pace instructions on walking performance in mild and moderate MS. It was found that the difference between usual and fastest speed decreases as the degree of ambulatory dysfunction increases. This finding was also evidenced by Kalron et al. [27], revealing a significant association between disability status and the walking speed reserve.

Regarding the T25FW performance in MS, a meta-analysis based on 50 studies quantified differences between pwMS and HC, as well as the influence of the disease severity and the MS types [28]. People with mild EDSS (EDSS3) performed considerably worse on the T25FW when compared to HC, with a mean difference of 2.4 (± 2.7) s the deficit in walking speed was 55%. Considering the disease severity based on the reviewed studies, pwMS with moderate and/or severe disability walked 51% slower than those with mild MS disability, spending an average of 5.5 (± 8.1) s more to complete the T25FW. Substantial worse T25FW performance was also found in the progressive MS course compared to the relapsing-remitting MS. The mean difference in time between the MS course was 13 ± 18 s. To understand the overall impact of

symptomatic treatment or rehabilitation on walking speed, it is important to highlight the clinically meaningful performance regarding walking speed in MS. Clinical meaningful change represents the amount of change or difference in walking speed that is not likely due to variations in trials or measurement errors and reflects the relevant impact in real-life activities. Studies regarding the T25FW in MS had identified the value of 20% as the minimal difference or change necessary to reflect real change above measurement error [23,26].

3.4. Walking middle distance

The evaluation of functional ambulation in MS clinical practice also includes longer distance walking tests to assess walking endurance. The most common functional capacity tests for walking long distance with evaluation of physical endurance are the 2-min walk test (2MWT) and the 6-min walk test (6MWT) [22,29]. Both tests were newly categorized as 'middle' distance, by Valet et al. [30], as clearly different from the T25FW (ICF short distance) and walking 1 km (ICF long distance). The 6MWT is a valid and reliable walking test and have been suggested as more convenient than the 500-m walk test to the ambulation scoring of the EDSS [29,31], while at the same time providing a score to all patients as opposed to the 500-m test which a substantial fraction of the patients will not be able to complete. Although the 6MWT has extensively been used as a primary ambulation outcome in rehabilitation trials [22], the feasibility of the 6MWT in neurological clinical practice has also been debated given that it is time consuming, while the strong association between the 2MWT and the 6MWT suggests that these two walking tests capture the same aspects of ambulation in well-functioning pwMS [32]. The ecological validity of the 2MWT and the 6MWT also showed that both walking tests similarly explained variances in real-life walking speed [25]. Furthermore, it has been shown that both tests, 2MWT and 6MWT, exhibit equivalent predictability for the number of steps taken in daily life. In addition, a similar high correlation coefficient ($r = -0.76$) was reported for the 2MWT and the 6MWT with the EDSS score [33]. The replacement of the 6MWT by the 2MWT would enhance the feasibility of testing, by bringing a briefer test that is easier to introduce in clinical practice [24,34]. However, in more disabled pwMS particularly, one may also miss information by the application of the 2MWT. Moreover, walking-related fatigability defined as slowing of walking speed over time requires a longer test targeting walking endurance, such as the 6MWT [35]. The decline in distance from the first to the sixth minute of the 6 MWT is the most reliable measure of walking fatigability. Leone et al. previously proposed a cutoff value of 15% decline in walking distance over time (DWI) [36], which may be adapted to 10% based on the study by Van Geel et al. study [37]. Walking-related fatigability is prevalent in up to half of persons with moderate to severe disability (EDSS>4), and intuitively of ecological relevance in daily life [36].

Regarding deficits in walking endurance, it has been shown that pwMS walk 61 ± 25% and 58.5 ± 26% slower during the 2MWT and the 6MWT compared to the predicted speed for HC, respectively [33]. Concerning the walking distance in long walking tests, a meta-analysis study [38] including the 6MWT identified that the mean distance walked by all MS participants included in the studies was approximately 450 ± 100 m, presenting a mean difference of about 170 ± 19 m compared to HC people. When considering the disease severity, pwMS with mild disability walked about 520 ± 90 m, while those with moderate or severe disability walked about 330 ± 110 m, revealing a mean difference of about 185 ± 9 m between groups [39]. Studies investigating day to day variability of long walk tests in MS have suggested a minimal detectable change in walking distance [23,40,41]. Feys et al. [42] investigated within-day variability in 102 pwMS and found this was approximately 19 and 54 m, in the 2MWT and 6MWT, respectively. Other studies also provide minimal detectable changes for the 6MWT of about 70 to 100 m [3,16,17]; however, the sample sizes are considerably smaller.

3.5. Perceived walking ability

The 12-item Multiple Sclerosis Walking Scale (MSWS-12) is a self-reported measure with 12 items which asks patients to rate the impact of MS on their walking and walking-related activities over 2 weeks, including questions about running, climbing stairs, effort, speed, need of support and balance. The MSWS-12 scale has an excellent test–retest reliability (ICC 0,94), internal consistency, and concurrent validity [43]. It has a cutoff of 75, has a sensibility of 52% and specificity of 82% in predicting fallers [11,43]. The clinically meaningful improvement is 8 to 10 [44].

4. Interventions to improve walking

Various pharmacological and non-pharmacological interventions have been developed for gait dysfunction.

4.1. Pharmacological treatment

Several symptomatic treatments may affect gait, by specialized drugs as fampridine or those prescribed to target symptoms such as spasticity and thereby gait dysfunction like baclofen, botulinum toxin, and cannabinoids.

Fampridine, or 4-aminopyridine, acts through several mechanisms of action in MS. Blockage of the exposed voltage-activated potassium (Kv) channels among demyelinated axons is considered the main mechanism [45]. Immune modulation and stimulation of the release of acetylcholine at the neuromuscular junction by direct activation of Ca^{2+} channels may be another pharmacodynamic pathway of fampridine in MS [46,47]. Fampridine was approved by the US Food and Drug Administration in 2010 for improving walking ability in patients with MS [48]. The medication is generally safe and with few adverse events being recorded in clinical trials. Those include urinary tract infections and seizures [30]. A prolonged-release form is preferred over direct release because of easier administration and a more constant serum level, leading to theoretically more stable effects and a lower risk of adverse effects [49].

Generally speaking, fampridine improves mobility in pwMS [50]. A positive effect on walking speed in short distances,

functional mobility, and perceived walking capacity has been consistently demonstrated. However, a meta-analysis showed that the effect on walking capacity on middle distances (i.e. as assessed by 2MWT or 6MWT) is not significant [30]. The effects of PR-fampridine on balance, coordination, and risk of fall are unclear, to date, although substantial improvements have been found on the six-spot step test which encompass coordination [50].

A responder versus non-responder approach is frequently used, both in research and clinical practice. This distinction assumes that some patients will benefit from the drug above a clinically significant threshold while others will not. As walking is the most studied outcome in fampridine research and it is only labeled clinical indication, responders are mainly defined based on walking-based outcomes. The 25FWT is the most commonly used test to determine the responder status. A patient performing better in the T25FW after an open trial period of fampridine is generally considered a responder. This approach was adopted in several seminal works on the topic [51–56]. Other studies relied on 6MWT[51] or MSWS-12 [57] to determine the responder status. Interestingly, a 6MWT below 211 m has been shown to be a good predictor of therapeutic responsiveness to PR-fampridine [58].

Gait dysfunction that is primarily a result of lower limb spasticity may be treated with medication like Baclofen, which is a derivative of γ aminobutyric acid (GABA) and it is a GABA B receptor and glycine receptor agonist that acts at spinal and supraspinal sites. The side effects of oral baclofen are dizziness, weakness, fatigue, and seizures. It is generally effective and tolerated. When spasticity is severe or the oral treatment dose is not tolerated, but control of spasticity could improve function and quality of life, intrathecal baclofen pump may be recommended. Intrathecal baclofen is administered by a programmable, subcutaneously implanted drug delivery system with a reservoir and catheter, delivering low doses of baclofen (<1% of the oral dose) [59], directly to the spinal cord. Intrathecal baclofen therapy should be considered when spasticity is inadequately managed by other treatments or side effects of such are unacceptable.

Clinical trials with oral and intrathecal baclofen for treating MS spasticity-related gait impairment are of low quality and the results are equivocal, because they focus on spasticity rather than walking, and only a small number of patients are ambulatory [59]. In the study of Saqid et al., the total number ambulatory patients (only 36) retained ambulatory function and 25% of the patients showed improvement in ambulatory function at 2 years or more of follow-up [60]. In the most recent and largest study, intrathecal baclofen improved spasticity outcome but had no statistical effect on the T25FW test over time in patients, but 72.3% of the patients remained ambulatory at 6 months [61,62]. As such, medical spasticity treatment with baclofen may preserve rather than improve walking over time.

The oromucosal spray is composed of delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD). The THC acts on cannabinoid receptor CB1 and CB2 as a partial agonist and it modulates the excitatory effects of glutamate and the inhibitory effects of GABA; and the CBD is a CB2 receptor antagonist. The THC:CBD oromucosal spray has shown improvement in the 10MW test [63–66], and a smaller pilot study with 20 pwMS reported spatial-temporal and kinematic gait parameter improvement [61,67].

When spasticity is isolated to one or few muscle groups, specific intramuscular injection of botulinum toxin may more effectively improve gait than oral or intrathecal medication [68]. Botulinum toxin binds presynaptically to high-affinity recognition sites on the cholinergic nerve terminal at the neuromuscular junction decreasing the release of acetylcholine producing a temporal neuromuscular denervation for an average of 3 months. Intramuscular phenol or alcohol injections can also be used for denervation of spastic muscles; however, their use is limited by permanent dysesthesias that can occur if either are injected near sensory nerve [68].

4.2. Exercise interventions

A review study from Pearson et al. [6] summarized the effects of different interventions on walking, suggesting that pooled data from aerobic, resistance training, cycling, home-based exercise, yoga, and combined training (aerobic and resistance training) showed significant results on walking capacity. Decrement of about 2 s was found on the time to complete the 10MWT; however, a non-significant result was found for the T25FW. In addition, when analyzing the modalities separately, the most effective exercise modality to improve walking speed was the combined training. The most effective exercise for the 6MWT was resistance training, improving the walked distance by about 55 m. Combined training showed the greatest improvement in 2MWT results, with an average improvement of about 25 m. Resistance training (i.e. strength training) promotes significant improvement in walking speed, ranging from 9% to 12% for the T25FW and 7.5% to 24.5% for the 10MWT. Improvements in walking endurance could also be found, ranging from 14 to 22 m on the 2MWT and from about 27 to 81 m on the 6MWT [69]. On the other hand, meta-analysis evaluating the effects of Pilates [70] and Yoga [71] on mobility did not show any evidence of improvement when compared to other interventions such as physical therapy sessions.

In terms of the impact of exercise on spatiotemporal and kinematics gait parameters, 6 months of an adapted exercise program including aerobic training (cycling) and resistance training provided an increment of 23.4% in walking speed was shown along with a significant increment in cadence and stride length, and decrement in stance phase (% gait cycle) and double support (% gait cycle). In addition, a trend of improvement in dynamic range of motion of the hip, knee, and ankle was shown [72]. Another study including resistance training also found that pwMS significantly decreased double support and stance phase, and increased the swing phase in percentage of the gait cycle. Furthermore, the less-affected leg presented increased stride and step length and plantar flexion, with decrement in toe clearance.

Considering the above-mentioned results from the reviews as well as from clinical trials, it is suggested that exercise interventions positively impact walking performance, and consequently contribute to the management of ambulation. It is

unclear to which extent exercise intensity matters when it is aimed to improve walking specifically [73]. Dalgas et al. [74] reported the summarized effects of exercise in MS proposing an exercise-induced postponement theory, where regular moderate-to-high intensity exercise could postpone the onset of clinical MS diagnosis and the occurrence and worsening of prominent symptoms. In addition, it was suggested that exercise should be prescribed from early stage to pwMS.

4.3. Task-oriented training (over ground, treadmill)

It is hypothesized that task-specific training improves mobility through changes in neural circuits within the central nervous system enhancing gait kinematics through the repetition of movements performed during walking [75]. The cortex responds to the demands of task-specific training by reorganizing the injured and uninjured parts of the brain. These neuroplastic changes stimulate neural output changing overall functional performance.

Task-specific training includes overground walking, walking treadmill, body-weight supported treadmill training (BWSTT), and robot-assisted gait training (RAGT) [76].

A meta-analysis by Robinson et al. [77] including only 40 participants from two studies demonstrates that treadmill training may be effective in improving mobility in pwMS who were able to walk (mild to moderate MS), by improving spatiotemporal measures of gait enhancing comfortable walking velocity and improving walking endurance. Training in studies was completed for 30 min, three times per week across an eight-week period. Treadmill training at a moderate to high intensity has been found to reduce energy expenditure and effort when walking and to improve cardiovascular function [78].

Body weight supported treadmill training (BWSTT) enables a patient with significant mobility impairment to walk on a treadmill while being partially supported by a harness, typically the patient is assisted by a therapist who guides the lower limbs through the gait cycle. Recently Robot-assisted gait training (RAGT) was developed to deliver consistently reproducible, high repetitive robot-guided movements [75]. Clinical robotic gait machines can be divided into grounded-end effectors and exoskeleton.

The grounded-end effectors have an electromechanical driven footplate that guides the feet and reproduces gait trajectories with a varying degree of support provided [79]. The exoskeleton is a system with robotic driven gait orthosis, where the knee and hip drive movements can be adjusted from 100% to 0% for either or both legs and can be in a system with body weight support and walk on a treadmill, such as in the Lokomat (Hocoma, Zurich; CH). The wearable exoskeletons assist individuals with lower limb paresis for ambulation and can be used as a gait training device and provides the opportunity to walk over ground in both indoor and outdoor environments. Most wearables exoskeleton devices such as Ekso and ReWalk utilize the user`s trunk movements to control externally powered gait [80].

The quality of movements during RAGT in terms of kinematics [81] and muscle activity [82] is not identical to the physiological gait, furthermore, RAGT is less energy-consuming and cardiorespiratory stressful than overground gait training [79,83,84]. Several studies revealed positive effects of RAGT for pwMS in gait speed [85,86], walking endurance [87,88], and kinematic [79,89]. The different studies show a positive but short-lasting effect, however, without a clear superiority of RAGT on traditional overground gait training [76,79,90]. Afzal et al. have shown in a small group study that wearable exoskeleton may increase self-selected gait speed and reduce metabolic expenditure during short distance walks in patients with high EDSS [80].

4.4. Novel strategies

In the last years, novel strategies such as motor imagery and rhythmic auditory stimulation have been developed to improve walking speed and distance in people with neurologic disorders. Motor imaginary is the mental execution of movements without any actual movement performance [91]. Two different perspectives can be adopted during motor imagery; the internal or first-person perspective (kinesthetic mode) where a person experiences his or her own body moving. The external or third-person (visual mode) perspective, the person imagining watches himself or herself [91,92].

For motor imagery of walking, individuals need to be ambulatory since there is a relationship between mental and physical execution of a movement [93]. It has been indicated that in people with motor impairment, the kinesthetic mode is more effective than the visual mode because of a more efficient motor learning due to sensory information [94].

Music-based interventions have been reported to positively impact cognitive and motor functions in the neurological population [95]. In this context, rhythm-based intervention is introduced, which consists of walking in the presence of auditory stimuli (music and metronome). In pwMS, a few studies have investigated the effect of rhythm-based interventions on gait kinematics and found that the intervention yielded positive results on gait kinematic [96,97]. Also, an intervention of 4 weeks comparing the effect of cued (using music and metronomes) and non-cued motor imagery in pwMS and walking impairment, revealed, in the cued motor-imagery conditions, improvements on walking, fatigue, and quality of life [98]. Furthermore, studies have been conducted in order to understand both the processes underlying walking to auditory-stimuli, such as entrainment and synchronization, as well as understanding the ingredients of applying such stimuli during walking for functional task-oriented training [99].

The daily life performance is associated with the simultaneous execution of motor and cognitive tasks. This can result in worsened performance on one or both tasks indicating cognitive-motor interference (CMI). The CMI is often quantified by the dual-task cost which is the percentage of change in dual-task performance relative to single-task performance [100]. Different approaches have been proposed on how training might improve dual-task performance.

Given the complexity of daily living activities and walking, rather a combinatory treatment approach is advocated. One model focuses on automatization of an individual task, thereby reducing attentional requirements. On the other side, the task-integration model proposed the two-task integration for improvement and in this context, the task needs to

be practiced simultaneously in a dual-task training. This dual-task training integrating cognitive tasks in the physical therapy program was shown to lead to improvements of walking during dual-task conditions [100].

4.5. Orthotic devices and assistive technology

In more disabled patients, a compensatory approach is needed. On the ICF environmental factor level, assistive technology is described as a means to improve functioning. Orthotic devices and functional electrical stimulation (FES) are two classes of assistive devices with the potential to mitigate specific deficits in the lower extremity which lead to a decrease in walking ability.

Orthoses are a broad range of devices applied outside the body to support, correct, or accommodate specific structures. An AFO consists of a footplate and a shin section, which is adapted to produce the optimal fit and function for the individual patient. Ankle-foot orthoses (AFO) are commonly described to minimize gait deficits caused by weakness or balance impairment, addressing problems such as decreased foot clearance in the swing phase of gait, reduced heel strike at initial contact and poor stability in the stance phase. AFO is effective for compensating weakness, restoring energy, and ankle/knee control. The literature on the effects of AFO in walking ability of pwMS is characterized by small samples. The research showed improved walking speeds, decreased energy consumption, static balance [101,102]. The hip flexion assist orthosis (HFAO) is designed to supplement the hip and knee flexors in the affected limb and additionally, dorsiflexion assistance is provided from the distal attachment. HFAO is safe and effective in pwMS with unilateral (or unilaterally predominant) hip flexor weakness, improving the gait speed during T25FW and walking distance in pwMS [103].

The functional electrical stimulation (FES) is a clinical application of a small electrical current to trigger a muscle contraction that is then incorporated into a functional activity. It has an effect as orthotic and a therapeutic effect. The orthotic effect is defined as the difference in walking ability at any given time between with FES and without FES conditions. The improvement, caused by FES use over time in function measured without the device is defined as the therapeutic effect [101]. Patients should be able to achieve neutral dorsiflexion (passively or assisted), skin tolerance to the electrodes, cognitive capacity, or support to manage technology and have realistic expectations [101]. The FES in pwMS with drop foot increased walking speed (T25FW), produced a reduction in energy expenditure and resulted in a significant improvement in patient-reported outcomes (MSWS-12)[11,104,105].

The literature in MS on the comparative use of FES versus AFO devices in the management of dropped foot is scarce. The available information in stroke and MS suggest a comparable effect of both methods on walking speed but with a slight increase in stability with AFO and better physical activity and obstacle avoidance with FES [105].

4.6. Assistive devices

Single-point canes enlarge the patient base support and are recommended to assist with even weight distribution during ambulation, helping patients with unstable gait and moderate balance control [11]. Quad canes provide more stability, however, decrease overall gait velocity and do not improve asymmetrical gait pattern [11,106]. Forearm crutches give a good base support, decreasing weight bearing on a single lower extremity in patients with mild to moderate balance deficit; however, the patient needs to have a good upper limb control. Finally, walkers provide the largest base of stability for increased stability during ambulation and are recommended for patients with moderate gait and balance deficits [11].

5. Conclusion

Walking impairment is frequently in pwMS and impacts the functional status, private and professional life and the quality of life. Gait disorders need to be identified and managed early in the course of MS, using a multimodal approach that needs to be adjusted over time based on the results of periodic assessments. Validated clinical outcome assessments that are frequently applied in pwMS include T25FW, 2MWT, 6MWT, and MSWS-12.

Finally, a growing body of evidence demonstrates the benefits of various pharmacological and non-pharmacological rehabilitation interventions on walking performance.

6. Expert opinion

Some degree of walking dysfunction is present in the majority of pwMS and contributes to disability and daily living restrictions. Walking can be categorized according to ICF where gait pattern classifies at body function level, while walking capacity and perceived ability are classified at activity level. The gait pattern can most often be characterized as paretic or spastic, cerebellar, sensory ataxia, or mixed, which have consequences for the subsequent symptomatic treatment and the applied rehabilitation strategy.

Accordingly, there are different walking evaluation methods that have been validated in pwMS. Clinical practice choices would, besides clinical observations of normal or compensatory walking, benefit from insights of the gait pattern by means of spatiotemporal (for example, step length versus cadence and step width) or kinematic (for example, knee flexion angle and push-off momentum) parameters measured by stationary or body-worn sensors. It would enhance personalization and specification of symptomatic treatment and would help refine the rehabilitation strategy. We recommend that routine clinical practice includes the assessment of short walking distance, preferably by means of the T25FW. We further recommend application of the 2MWT if rehabilitation has been undertaken to further expand the understanding of the clinical impact of rehabilitation as the 2MWT has shown robust psychometric properties including better responsiveness than the T25FW. Furthermore, the 6MWT is advocated in case of suspicion of walking-related fatigability. In addition to objective walking outcomes, the

self-reported MSWS-12 is applicable across the disability spectrum and further seems to be a very sensitive outcome in the patients with mild MS. For all tests, values of clinically meaningful changes are available and should be integrated when interpreting the results in both clinical practice and research.

Symptomatic treatment focuses on impairments and is effective at improving walking speed and distance while at the same time also having the potential to normalize the gait pattern in pwMS. Subsequently, relevant interventions targeting walking should be included in multi-disciplinary treatment programs. The most well-established interventions to increase walking speed and distance in pwMS, that are underpinned by evidence, are exercise and task-specific training. Positive effects on walking following exercise and task-specific training are also seen in more disabled MS patients and in progressive. For the latter, compensatory aids are needed and interventions such as FES, body weight supported walking or robot-assisted training may be considered although the effects hereof need to be further elucidated. Moreover, the existing (positive) evidence supporting the use of these interventions needs to be cautiously interpreted, as studies were often performed in selected patient groups without major comorbidities, high levels of fatigue, or cognitive deficits.

In the latter perspective, novel interventional strategies such as rhythmic facilitation or integrated cognitive-motor training have emerged and proven potentially useful in clinical practice.

Next steps are to expand our understanding of whether effects are temporary or may lead to neuroplastic changes that are more sustainable. A further perspective for the future includes the potential synergistic effect of combining pharmacological interventions (e.g. Fampridine) with different interventions targeting walking in pwMS. Interestingly, preliminary evidence suggests superiority of such combined interventions, but further studies elucidating the interaction between medication and physical interventions targeting walking are warranted.

Finally, not addressed in this review, is the importance of persons practicing exercise and walking during daily life, while being on their own. Moreover, further development of methodologies to enhance the implementation of a physically healthy lifestyle should also address the importance of social support and (remote) supervision.

Declaration of interest

B Soler has received travel grants from Biogen Idec, Merck Serono, Technofarma, and/or teaching honorary from Merck. P Feys has provided consultancy to Neurocompass and Biogen Idec. P Feys is an editorial board member of MSJ and NNR journal. U Dalgas has received research support, travel grants, and/or teaching honorary from Biogen Idec, Merck Serono, Novartis, Bayer Schering, and Sanofi Aventis as well as honoraria from serving on scientific advisory boards of Biogen Idec and Genzyme. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or conflict with the subject matter or materials discussed in this manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

This paper was not funded.

ORCID

Bernardita Soler http://orcid.org/0000-0002-8143-4497

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THE IMPACT OF PHYSICAL FUNCTIONS ON DEPRESSIVE SYMPTOMS IN PEOPLE WITH MULTIPLE SCLEROSIS

Journal:	*Arquivos de Neuro-Psiquiatria*
Manuscript ID	ANP-2020-0001.R2
Manuscript Type:	Original Article
Date Submitted by the Author:	30-May-2020
Complete List of Authors:	Tauil, Carlos Bernardo; Universidade de Brasília, Ciências Médicas Ramari, Cintia; Universidade de Brasília, Laboratório do Movimento Humano Brasil, Erica; Hospital de Base do Distrito Federal, Psicologia Silva, Flávia; Hospital de Base do Distrito Federal, Psicologia Gomes, Jacqueline; Hospital de Base do Distrito Federal Von Glehn, Felipe; Universidade de Brasília, Ciências Médicas de David, Ana; Universidade de Brasília, Laboratório do Movimento Humano Brandão, Carlos; Universidade Estadual de Campinas, Unidade de Neuroimunologia Santos, Leonilda; Universidade Estadual de Campinas, Genética, Evolução e Bioagentes - Unidade de Neuroimunologia Santos-Neto, Leopoldo; Universidade de Brasília, Ciências Médicas
Keyword:	Multiple sclerosis, Depression, Physical functions, Walking, Gait

THE IMPACT OF PHYSICAL FUNCTIONS ON DEPRESSIVE SYMPTOMS IN PEOPLE WITH MULTIPLE SCLEROSIS

O impacto das funções físicas nos sintomas depressivos em pessoas com esclerose múltipla

Cabeçalho: Tauil CB et al. Multiple sclerosis: physical functions and depression.

Carlos B. TAUIL[1]*, Cintia RAMARI[2]*, Flávia M. da SILVA[3], Erica BRASIL[3], Ana de DAVID, Jaqueline R.A.A. GOMES[3], Felipe von GLEHN[1], Carlos O. BRANDÃO[4], Leonilda M.B. dos SANTOS[4] and Leopoldo dos SANTOS-NETO[1]

[1] Universidade de Brasília (UnB), Faculdade de Medicina, Departamento de Ciências Médicas, Brasília DF, Brasil.
[2] Universidade de Brasília (UnB), Faculdade de Educação Física, Laboratório do Movimento Humano, Brasília DF, Brasil.
[3] Hospital de Base (HBDF), Brasília - DF, Brasil.
[4] Universidade de Campinas (Unicamp), Instituto de Biologia, Departamento de Genética, Evolução e Bioagentes, Unidade de Neuroimunologia, Campinas SP, Brasil.

* The authors contributed equally to this study.

Correspondence: Carlos Tauil; Email: cbtauil@gmail.com.

ORCID:
Carlos B. Tauil: 0000-0003-1137-2398
Jacqueline R. A. A. Gomes: 0000-0002-7243-4073
Felipe Von Glehn: 0000-0002-1004-7641
Carlos O. Brandão: 0000-0002-4898-5916
Leonilda M. B. dos Santos: 0000-0002-3600-9205
Leopoldo L. dos Santos-Neto: 0000-0002-8060-6111

Conflict of interest: There is no conflict of interest to declare

ABSTRACT

Background: Multiple sclerosis (MS) is an immune-mediated disease that affects the central nervous system. The disease impact transcends physical functions and also extends to impairments in psychological functions. Approximately 50% of people with MS develop depressive symptoms during their life time. Studies have shown that depressive symptoms could predicts impairment of physical functions. However, the prediction of depressive symptoms based on an abroad objective measures of physical functions is still necessary.

Objectives: To compare physical functions between people with MS presenting and do not presenting depressive symptoms, and, in addition, to identify predictors of depressive symptoms using objective measures of physical functions.

Methods: Twenty-six people with MS were included in this cross-sectional study. Anxiety and/or depressive symptoms were assessed by the Beck Depression Inventory – II (BDI-II) and by the Hospital Anxiety and Depression Scale. Physical functions outputs included: the nine-hole peg test, knee muscle strength, balance control, the timed up and go test and the six-minute walk test. Perceived fatigue was measured using the Borg scale.

Results: The prevalence of depressive symptoms was 42% in people with MS. Balance control during a more challenging task was impaired in depressive symptomatic people with MS. Balance could explain 21 – 24% of the variance in depressive symptoms. The 6MWT and the TUG presented a trend of significance explaining 16% of the variance in the BDI-II score. **Conclusions:** impairment in physical functions are potential predictors of depressive symptoms in people with MS. Exercise interventions targeting the improvement of physical functions alongside the treatment of depressive symptoms and conventional medical treatment are suggested.

Key words: Multiple Sclerosis, Depression, Physical Functions, Balance, Walking.

RESUMO

Fundamentos: A esclerose múltipla (EM) é uma doença imunomediada que afeta o sistema nervoso central. O impacto da doença transcende as funções físicas e também se estende a deficiências nas funções psicológicas. Aproximadamente 50% das pessoas com EM desenvolvem sintomas depressivos durante a vida. Estudos demonstraram que sintomas depressivos podem predizer comprometimento das funções físicas. No entanto, a previsão de sintomas depressivos com base em medidas objetivas das funções físicas ainda é necessária.

Objetivos: comparar funções físicas entre pessoas com EM que apresentam ou não apresentam sintomas depressivos e, além disso, identificar preditores de sintomas depressivos usando medidas objetivas de funções físicas.

Métodos: Vinte e seis pessoas com EM foram incluídas neste estudo transversal. A ansiedade e / ou sintomas depressivos foram avaliadas pelo Inventário de Depressão de Beck - II (BDI-II) e pela Escala Hospitalar de Ansiedade e Depressão. Os resultados das funções físicas incluíram: teste de PEG, de nove buracos, força muscular do joelho, controle de equilíbrio, teste de aceleração e aceleração e teste de caminhada de seis minutos. A fadiga percebida foi medida usando a escala de Borg.

Resultados: A prevalência de sintomas depressivos foi de 42% em pessoas com EM. O controle do equilíbrio durante uma tarefa mais desafiadora foi prejudicado em pessoas com EM que apresentaram sintomas depressivos. O equilíbrio pode explicar 21 - 24% da variação nos sintomas depressivos. O TC6 e o TUG apresentaram uma tendência de significância que explica 16% da variância no escore do BDI-II.

Conclusões: o comprometimento das funções físicas é um potencial preditor dos sintomas depressivos em pessoas com EM. São sugeridas intervenções de exercícios físicos visando a melhoria das funções físicas, juntamente com o tratamento dos sintomas depressivos e tratamento médico convencional.

Palavras-chave: Esclerose Múltipla, Depressão, Funções Físicas, Equilíbrio, Caminhada.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, immune-mediated disease that affects the central nervous system. The accumulation of demyelinating lesions in different areas of the white and grey matter of the brain and the spinal cord leads to a heterogeneous clinical manifestations of the MS disease[1]. Impairment of physical and cognitive functions increase as the disease progress, being walking and thinking/memory the most valuable functions according to the patients and physician's opinion[2]. However, the disease impact transcends physical functions and extends to impairments in psychological, cognitive, visual, fatigue, among others domains[3]. Health-related quality of life of people with MS seems to decrease as the perception in the degree of limitation of physical and cognitive functions increase, affecting the emotional state, social functioning and, consequently, mental health[4,5].

About 25 to 50% of people with MS develop depressive symptoms during their life time, a number two to five times higher compared to the general population[6]. However, although these symptoms are common, they are often underdiagnosed[7], and the impacts of the disease, especially for the youngers, produce feelings of helplessness and low self-efficacy in MS patients[7,8]. An study [7] investigating factors associated with anxiety and depressive symptoms, using a multivariate model in MS, has suggested that the factors could be grouped as: 1) the cause of an increase of anxiety or depressive symptoms (e.g. male sex, concussion, other medical condition); 2) the result of anxiety or depressive symptoms (e. g. use of antidepressant or anxiolytic-sedative medications); 3) both, a cause and the result (e.g., less physical activity, being unemployed); 4) correlate of anxiety or depressive symptoms or part of the same disease process (e.g. disability).

Regarding the impairment of physical functions and the impact on anxiety and/or depressive symptoms in MS, decrement in subjective walking capacity seems to predict change in depressive symptoms at 2-year follow up[9]. Although baseline subjective walking capacity, measured by the Multiple Sclerosis Walk Scale (MSWS-12), have been associated with depressive symptoms [9], and explained approximately 20% of the variance related to the symptoms [10]. On the other hand, objective short walking tests were not

significantly different between depressed and non-depressed people with MS[11], particularly when controlling for age, gender and EDSS[10]. However, self-efficacy for function revealed to be associated with walking speed (timed 25-foot walk test, T25FW) and endurance (6-minute walk test, 6MWT)[12], suggesting the importance of mental health related to confidence for performing activities of daily living. Furthermore, a study investigating depressive symptoms as predictor of subjective balance control showed that depressive symptoms explained 11 - 17 % of the variance in balance, suggesting that as the symptoms increase, the capacity of performing functional activities that require balance decrease [13].

Once disability, usually measured by walking capacity along with sensory functions, which are also related to balance, is a correlate of anxiety and/or depressive symptoms, and might be a part of the same disease process, it seems necessary to investigate potential predictors of anxiety and/or depressive symptoms concerning to physical functions. Then, the development of strategies such as physical exercise and/or pharmacologic interventions focusing on the improvement of these physical determinants could be an aid for the treatment of depressive symptoms in people with MS. Thus, the aims of this study were to compare physical functions between people with MS presenting and not-presenting depressive symptoms, and, in addition, to identify predictors of anxiety and depressive symptoms using objective measures of physical functions.

METHODS

Twenty-six people with MS (24 women/2 men) were included in this cross-sectional study. The written informed consent was obtained prior to the procedures and the Ethics Committee from the Department of Health/ Brasília - Brazil approved the study (CAAE: 67098217.5.0000.5553). Inclusion criteria were being ≥18 years old; having the confirmed diagnosis of relapsing-remitting (RR) MS course by a neurologist, according to the revised McDonald criteria[14]; being capable to perform the 6MWT; being relapse free over the past 30 days. Exclusion criteria were being unable to understand the motor tests commands;

being pregnant or having any infectious, neoplastic and psychiatric diseases (except for mood disorders); receiving treatment with other psychiatric medications, such as antipsychotics and anxiolytics; having non-controlled chronical medical conditions such as hypertension, diabetes and cardiac conditions; and presenting other neurologic conditions in addition to MS.

Disability status was scored using the expanded disability status scale (EDSS) by a trained neurologist[15].

Anxiety and/or depressive symptoms scales

Anxiety and/or depressive symptoms were assessed by two neuropsychologists using two validated scales: 1) The Beck Depression Inventory-II (BDI-II), which is a self-report scale with 21 items that add together to give a total BDI score ranging from 0 to 63 points. Each item scoring from 0 to 3[16,17]; 2) The Hospital Anxiety and Depression Scale, which rates two components - anxiety (HADS-A) and depression (HADS-D), each consisting of 7 items, yielding a range of scores from 0 to 21 for each item[18].

Physical functions

Manual dexterity was evaluated using the nine-hole peg test (NHPT), the average of the time taken to perform the test twice was used for the analysis[19].

Dynamic muscle strength from the knee extensor and flexor muscles were assessed by an isokinetic dynamometer (Biodex Medical Systems 3, Inc., USA)[20]. The range of motion was kept within 0–80° for the knee joint. Four bilateral isokinetic (concentric/concentric) extension and flexion of the knee joint were performed at 60 degrees per second. The maximum value obtained between the two legs was kept for the analysis.

Balance control was based upon the displacement of the center of pressure (COP) quantified using a force platform (AccuSway Plus, AMTI Inc, USA). Participants were instructed to stand upright and barefoot on the force platform (stable surface - COP_{stable}) and on a plastic foam placed on the platform (unstable surface - COP_{foam}), keep their eyes open and look at a point located at a 1.5 meters of distance. The data were acquired during three trials of 30-seconds with 60-seconds of rest. A sampling rate of 100 Hz and a

Butterworth digital filter with cutoff frequency of 10 Hz were used. The COP velocity parameter was used for the analysis[21].

Mobility was evaluated through the timed up and go test (TUG). Patients were instructed to stand up from a standardized chair with arms crossed on the chest, walk three meters, turn around, walk back and sit down on the chair. The test was performed twice and the mean time in seconds of two attempts was used for the analysis[22].

The 6MWT was used to evaluate walking endurance[23]. Participants were instructed to walk as fast and as far as possible without rest or encouragement for 6 minutes. The 6MWT was completed within a single corridor measuring ten-meter in length, with cones placed on opposite ends, while performing 180° turns around the cones.

Subjective fatigue was measured by the 15-point (6 - 20) Borg scale[24]. The perceived fatigue concerning to the overall physical fatigue sensation was asked prior to the 6MWT and after every minute of the test. The rate of perceived exertion in percentage was calculated using the values reported instantaneously after the 6MWT and before the test.

Statistical analyses

In order to perform the analysis between people with MS presenting and not presenting depressive symptoms, the depressive symptoms status was identified using a cut-off score of 13 on the BDI-II (17). As this cut-off score seems to screen for about 70% of MS patients with significant depressive symptoms in ambulatory people [25]. People with MS with the BDI score ≤ 13 were classified as non-symptomatic for depression, while BDI-II score > 13 was accounted for a symptomatic for depressive state.

Statistical analyses were performed using descriptive statistics and data are presented as mean and 95% confidence interval (95% CI). Shapiro-Wilk test examined normality of the data. Distribution of data was also visually checked with box-plots, q-q-plots, histograms and dot-plots. In order to perform parametric tests and the linear regression analysis, the data from the NHPT, TUG and COP $_{stable}$ and COP $_{foam}$ were transformed ($X_i = 1/x_i$ ^2). To perform comparisons between groups (depressive non-symptomatic and symptomatic) the unpaired t-test was used. Simple linear regression analysis was carried out

to examine potential associations between outcomes of depressive symptoms and physical functions. The significance of the R-squared values was used to identify the predictors of depressive symptoms. The Pearson correlation test was graphically represented for the significant predictors. Level of statistical significance was set at $p \leq 0.05$, and trend as $0.05 < p < 0.10$. All data analyses were performed using the SPSS program (SPSS 13.0, SPSS Inc., USA).

RESULTS

As shown in table 1, no differences in clinical characteristics could be found between depressive non-symptomatic and symptomatic people with MS. Concerning to mental health, anxiety status (HADS-A) did not differ between groups, and the HADS-D score was significantly higher for the depressive symptomatic participants classified by the BDI-II. Comparisons in physical functions revealed a significant higher COP velocity for depressive symptomatic people with MS during the test performed on an unstable surface (COP_{foam}). In addition, a trend of significance was detected in the 6MWT between groups. No statistical significant differences between depressive non-symptomatic and symptomatic participants could be found in manual dexterity, muscle strength, balance on a stable surface, mobility and in the increment of perceived exertion. Tables 2 and 3 present the results from the simple linear regression analysis performed between clinical characteristics / physical functions and the BDI-II, and the HADS-D, respectively. COP_{foam} significantly explained 21% of variance in the BDI-II score and 24% of the variance in the HADS-D. Furthermore, TUG and 6MWT presented a trend of significance, explaining 16% of the variance in the BDI-II. No statistical significant associations were found between any clinical characteristics and the BDI-II and HADS-D scores. Simple regression results between clinical characteristics / physical functions and HADS-A can be found in the supplementary data.

Figure 1 graphically represents the significant association between balance and the BDI-II scores.

DISCUSSION

The main finding of the present study is that the output from a more challenge balance test - COP $_{foam}$, could significantly predict depressive symptoms explaining 21% and 24% of the variance in the BDI-II and in the HADS-D. In addition, COP $_{foam}$ was statistically different between depressive non-symptomatic and symptomatic people with MS. The prevalence of depression was 42% in our sample of MS patients.

Studies investigating the associations between physical functions and mental health have mostly been focused on how mental health, evaluated by mood disorders and self-efficacy, could predict walking capacity [10,12], activities of daily living [11], self-reported physical activity [5] and balance [13]. In this current study, balance control during a more challenging task was a significant predictor of depressive symptoms, suggesting that impairment in physical function such as dynamic balance can affect mental health. Our results corroborate in part with the findings from Alghwiri et al. study[13], where associations between depressive symptoms and balance could also be found. However, in their study, balance was measured by the subjective Activities Specific Balance Confidence Scale – ABC, and by the Berg Balance Scale – BBS, suggesting that the ability to perform dynamic balance tasks during the activities of daily living is affected by the depressive symptoms level. On the other hand, our study also showed that, a more precise and challenging method of balance control using a force platform and a plastic foam, could generate an output capable of predicting depressive symptoms. Considering our results along with the results from Alghwiri et al., we could imply that the sensory systems responsible for balance control is impaired in people with MS, consequently, affecting the independency of performing activities of daily living that comprises dynamic balance. Altogether, the loss of independency can affect the mental health of people with MS[8,11], as well as, low self-efficacy generated by depressive symptoms can affect physical functions such as walking[9], physical activity and social functioning[5].

Concerning to the others aspects of physical function that could predict depressive symptoms, although no statistical significance was found for any of the other functions, a trend of significance could be found regarding the 6MWT.

The 6MWT distance presented to be slightly lower for depressive symptomatic people with MS, and it could explain 16% of the variance in the depressive symptoms. In addition, TUG test, which involves both ambulation and dynamic balance, also presented a trend of significance for predicting depressive symptoms. A study from Kalron et al.[10] showed that depressed people with MS walked significantly slower, however the differences were no longer significant when controlling for EDSS score, age and gender. In addition, significant differences could be found between groups (depressed and non-depressed) regarding the MSWS-12, even when controlling for the same parameters. The short walk test performed in their study may not comprised the difficulties presented in ambulation during the daily life such as fatigability, factor that the MSWS-12 could be more sensitive for. Furthermore, results from another study [9] suggested that MSWS-12 could not only predict depressive symptoms as well as predict the worsening of the symptoms after 2 years. However, it is necessary to keep identifying more objective tests regarding to physical functions in order to target the interventions strategies. As shown in another study investigating associations between self-efficacy and walking[12], the 6MWT was significantly associated with self-efficacy, suggesting the importance of including measures of walking endurance in future studies investigating the impact of physical functions on depressive symptoms.

Practical applications

In the present study, the BDI-II revealed to be a more sensitive scale to identify depressive symptoms in people with MS, although differences could be found between depressive non-symptomatic and symptomatic patients regarding to the HADS-D, perhaps confirming the consistency of the scales. Concerning to the tests of physical functions and the outputs capable of predicting depressive symptoms, we suggest the use of more objective tests that can predict the difficulties of performing activities of the daily living and the lower levels of physical activity. Future studies should consider to include the motor-fatigability tests [26-28], the sit-to-stand test [29,30], the six-spot step test [31], among others [32]. Furthermore, we suggest the use of strategies to improve physical functions, such as rehabilitation and exercise interventions targeting adaptations in the neuromuscular system such as resistance training, as well as

dynamic balance training and aerobic exercise. In this context, and considering the high impact of exercise in people of MS, it should be prescribed from early stage of the MS disease alongside conventional medical treatment[33]. Not less important, it is important to highlight the importance of appropriate detection and treatment of depressive symptoms in people with MS.

Limitations of the study

Although this is the first study, from our knowledge, to include an abroad measures of physical functions, and to identify the COP output from a gold standard balance test that predicts depressive symptom, it also presents some limitations. The sample size may have limited the comparisons between groups. The selection of the participants was not based on their depressive symptoms status or on their disability. Most of the patients were well functioning, and classified with mild MS. Finally, as a cross-sectional study, it could not allow the discussion regarding the causality of physical functions on mental health.

CONCLUSIONS

The prevalence of people with MS presenting depressive symptoms was 42%. Balance control during a more challenging task was impaired in depressive symptomatic people with MS. Balance could explain 21 – 24% of the variance in depressive symptoms. The 6MWT and the TUG presented a trend of significance explaining 16% of the variance in the BDI-II score. Concluding, impairment in physical functions are potential predictors of depressive symptoms in people with MS. Exercise interventions targeting the improvement of physical functions alongside the treatment of depressive symptoms and conventional medical treatment are suggested.

Compliance with ethical standards

Conflict of interest: All authors declare that they have no conflict of interest.

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Table 1. *Descriptive clinical characteristics, mental health and physical functions of people with multiple sclerosis. Comparisons between groups of depressive symptoms status.*

Variables	**All**	**Non-symptomatic**	**Symptomatic**
Clinical			
N (female/male)	26 (24/2)	15 (15/0)	11 (9/2)
Age, y	36.2 (32.4 : 40)	36.5 (30.5 : 42.5)	35.9 (31.2 : 40.5)
Weight, kg	63 (56.6 : 69.5)	59.1 (52.9 : 65.4)	69.6 (54.8 : 84.4)
Height, cm	160.2 (157 : 163.3)	158.8 (156 : 161.6)	163 (154 : 172)
Disease duration, y	6.1 (4.3 : 7.9)	5.6 (3.2 : 7.9)	4.1 (1.1 : 7.1)
EDSS score	2.6 (2.1 - 3.1)	2.3 (1.8 : 2.8)	3.2 (2 : 4.3)
Mental Health			
HADS-A	8.5 (6.9 : 10.1)	7.7 (5.2 :10.2)	9.7 (7.8 : 11.6)
HADS - D	6 (4.6 : 7.4)	4.5 (3.2 : 5.8)	8.1 (5.4 : 10.7) [a]
BDI-II	13.7 (10.2 : 17.1)	8.1 (6.3 : 10)	21.2 (16.2 : 26.2) [a]
Physical Functions			
NHPT, s	19.7 (18.4 : 21)	19.1 (17.5 : 20.7)	20.5 (18 : 23.1)
PT_{KE}, N.m	107 (94.1 : 119)	106.2 (91.6 : 120.9)	108 (85 : 130.8)
PT_{KF}, N.m	47 (39.2 : 54.9)	49.1 (39.5 : 58.8)	44.6 (30 : 59.2)
COP_{stable}, cm/s	1.17 (0.93 : 1.41)	1.02 (0.90 : 1.12)	1.37 (0.81 : 1.93)
COP_{foam}, cm/s	2.58 (2.2 : 3)	2.18 (1.9 : 2.6)	3.12 (2.3 : 4) [a]
TUG, s	8.9 (6.2 : 11.4)	7.2 (6.6 : 7.7)	11.2 (4.4 : 18)
6MWT, m	481 (444.5 : 517.4)	503.8 (469.5 : 538.2)	443.8 (359.3 : 528.2) [a]
RPE, %	33 (18 : 49)	30 (7 : 54)	37 (18 : 57)

Abbreviations: *EDSS, expanded disability status scale. HADS-A, hospital anxiety and depression scale - anxiety. HADS-D, hospital anxiety and depression scale - depression. BDI-II, beck depression inventory-II. NHPT, nine-hole peg test.* PT_{KE} *peak torque knee extensor.* PT_{KF} *peak torque knee flexor. COP, center of pressure. TUG, the timed up and go test. 6MWT, six-minute walk test. RPE, rate of perceived exertion. Statistical significance ($p \leq 0.05$) and trends ($0.05 < p < 0.10$, shown in italic) are denoted by a: different from depressive non-symptomatic people with multiple sclerosis.*

Table 2. *Coefficients from the simple linear regression analysis including clinical characteristics / physical functions and the beck depression inventory (BDI-II).*

Variable	*β*	*95% CI*	*P-value*	*R-squared*
Age	-0.04	-0.40 : 0.32	0.81	0.002
Disease duration	-0.08	-0.99 : 0.66	0.69	0.007
EDSS	0.34	-0.41 : 4.45	0.10	0.11
NHPT	-0.28	-6689 : 1499	0.20	0.08
Peak Torque $_{KE}$	-0.25	-0.21 : 0.05	0.22	0.06
Peak Torque $_{KF}$	-0.34	-0.36 : 0.03	0.10	0.11
COP $_{stable}$	-0.18	-10.6 : 4.2	0.38	0.03
COP $_{foam}$	-0.46	-56.3 : -4.9	**0.02**	0.21
TUG	-0.40	-868.6 : 21.3	*0.06*	0.16
6MWT	-0.40	-0.07 : 0.003	*0.06*	0.16
RPE	0.33	-1.5 : 9.8	0.14	0.11

Abbreviations: *EDSS, expanded disability status scale. NHPT, nine-hole peg test. PT $_{KE,}$ peak torque knee extensor. PT $_{KF,}$ peak torque knee flexor. COP, center of pressure. TUG, the timed up and go test. 6MWT, six-minute walk test. RPE, rate of perceived exertion. Statistical significance is denoted by the bold letter and the trend denoted by the italic letter of p-values.*

Table 3. *Coefficients from the simple linear regression analysis including clinical characteristics / physical functions and the hospital anxiety and depression scale - depression (HADS-D).*

Variable	*β*	*95% CI*	*P-value*	*R-squared*
Age	0.14	-0.10 : 0.20	0.49	0.02
Disease duration	-0.21	-0.50 : 0.16	0.29	0.04
EDSS	0.15	-0.75 : 1.6	0.47	0.02
NHPT	-0.23	-2870 : 924.2	0.29	0.05
Peak Torque $_{KE}$	-0.25	-0.08 : 0.02	0.24	0.06
Peak Torque $_{KF}$	-0.30	-0.14 : 0.02	0.15	0.09
COP $_{stable}$	-0.10	-3.9 : 2.4	0.62	0.01
COP $_{foam}$	-0.49	-24.9 : -2.1	**0.01**	0.24
TUG	-0.36	-381 : 33.2	*0.09*	0.13
6MWT	-0.36	-0.03 : 0.004	0.10	0.13
RPE	0.22	-1.5 : 4.2	0.32	0.05

Abbreviations: *EDSS, expanded disability status scale. NHPT, nine-hole peg test. PT $_{KE,}$ peak torque knee extensor. PT $_{KF,}$ peak torque knee flexor. COP, center of pressure. TUG, the timed up and go test. 6MWT, six-minute walk test. RPE, rate of perceived exertion. Statistical significance is denoted by the bold letter and the trend denoted by the italic letter of p-values.*

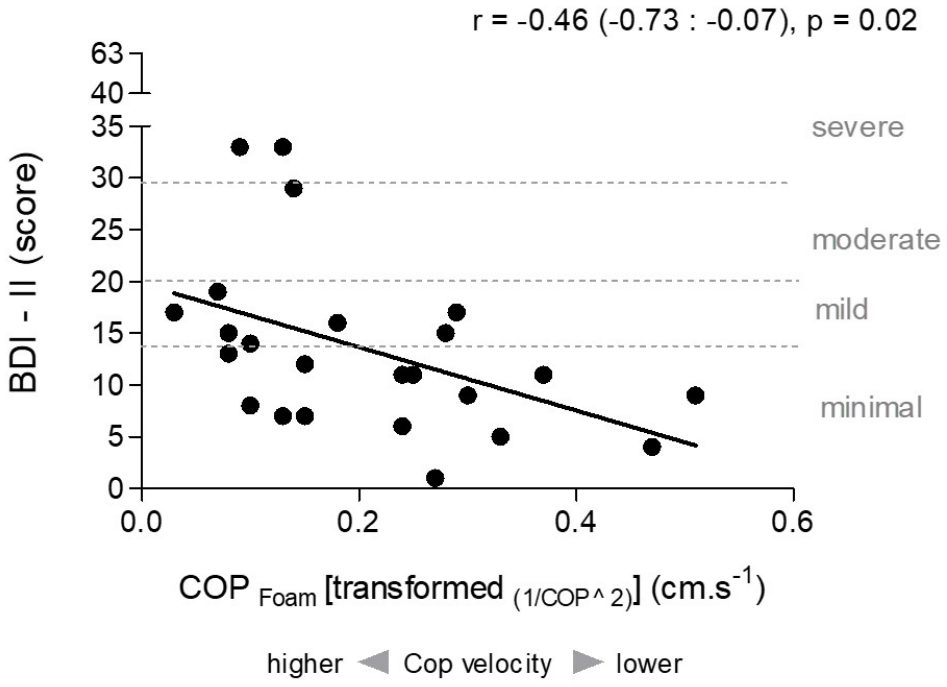

Figure 1. Association between center of pressure on an unstable surface (COP foam) and the beck depression inventory - II (BDI-II). For note, the regression between COP foam was performed using a second degree hyperbolic transformation (1/COP foam ^2). Result has to be interpreted with caution, as the values of velocity are inverted. The grey legend on the right means the degree of depression according to the BDI-II.

254x190mm (96 x 96 DPI)