Lower extremity muscle power – A critical determinant of physical function in aging and multiple sclerosis

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ARTICLE INFO

Section editor: Emanuele Marzetti

Keywords:
Multiple sclerosis
Aging
Muscle power
Lower extremity physical function

ABSTRACT

Background and purpose: In aging, lower extremity muscle power is undoubtedly one of the most important parameters of neuromuscular function implicating lower extremity physical function (e.g. walking capacity). However, no previous studies have examined the combined effects of aging and multiple sclerosis (MS) on lower extremity muscle power concomitant with lower extremity physical function. The aim of this cross-sectional study was to examine potential decrements in pwMS vs. healthy controls (HC) across the adult lifespan in these outcomes.

Methods: In the present explorative cross-sectional study, n = 42 pwMS (females n = 29 (69%); age = 53 ± 12 years (mean ± SD), range 31–78; patient determined disease steps score = 3.7 ± 1.7, range 0–7) and n = 49 age-matched HC (females n = 34 (69%); age = 56 ± 16 years, range 24–78) were enrolled, and divided into groups of young (≤ 44 years), middle-aged (45–59 years), and old (> 60 years). Muscle power was obtained from bilateral leg press (PowLegPressPeak) and maximal chair rise (PowChairRise) using a linear encoder. Associations were assessed between muscle power and measurements of lower extremity physical function (5 x sit-to-stand (STS); timed 25-foot-walk-test (T25FWT)).

Results: Muscle power was reduced in pwMS vs. HC (PowLegPressPeak –23% [−34;−12] % (mean[95%CI]); PowChairRise –26% [−35;−17] %) and was negatively associated with advanced age in both pwMS (decline per decade –0.40 W.kg⁻¹ and –2.53 W.kg⁻¹, respectively) and HC (decline per decade –0.42 W.kg⁻¹ and –2.03 W.kg⁻¹, respectively). Muscle power was strongly associated with physical function in pwMS (r².range = 0.45–0.61, p < 0.01) yet only moderately associated in HC (r².range = 0.18–0.39, p < 0.01).

Conclusion: The combined effects of MS and aging reveal substantial decrements in lower extremity muscle power that is accompanied by (and strongly associated with) decrements in lower extremity physical function. Consequently, lower extremity muscle power should be viewed as a clinically important factor (i.e. a critical determinant of lower extremity physical function) in pwMS. We propose that lower extremity muscle power should be specifically targeted by preventive and rehabilitative exercise strategies, especially in older pwMS.

1. Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system (Compston and Coles, 2008), believed to be caused by a complex interaction of both genetic and environmental factors (Compston and Coles, 2008; Filippi et al., 2018; Lassmann, 2013). The neurodegenerative consequences accompanying persons with multiple sclerosis (pwMS) are evident from the alterations observed in neural transmission throughout the central and peripheral nervous system ultimately affecting neuromuscular function i.e. the nerve-muscle interaction responsible for motor functioning (Lassmann, 2013; Vucic et al., 2010; Mamoe et al., 2020). Indeed, decrements in lower extremity muscle strength in pwMS (i.e. reduced levels of isometric, dynamic, and explosive muscle strength) compared to healthy
controls (HC) has frequently been reported (Jorgensen et al., 2017; Scott et al., 2011; Sieljacks et al., 2020), with the most pronounced decrements being observed during fast muscle contractions. These decrements in lower extremity muscle strength are well-known to be accompanied by/associated with decrements in physical function including daily physical tasks such as walking, stair climbing, and chair rise (Sieljacks et al., 2020; Ramari et al., 2020; Schvid et al., 1999; Thoumie et al., 2005). Preliminary study findings suggest that the velocity of muscle contraction may influence these associations, i.e. with greater implications at faster muscle contractions (Jorgensen et al., 2017; Sieljacks et al., 2020). Nonetheless, lower extremity muscle power (defined as the product of force production and contraction velocity) has rarely been examined in pwMS, although it may be more prone to decrements and thus stronger associated with physical function than muscle strength alone. This notion was supported by Chung and colleagues who reported decrements in knee extensor muscle power in pwMS compared to HC exceeding that observed in muscle force (∼strength) (Chung et al., 2008). Muscle power may therefore potentially serve as a particularly useful outcome reflecting the neurodegenerative consequences of MS.

Reassembling the observations in pwMS, albeit to a smaller extent, the biological process of aging are also accompanied by numerous neurodegenerative consequences (Borziosa et al., 2020; Hepple and Rice, 2016) along with decrements in lower extremity muscle strength and physical function (Sieljacks et al., 2020; Byrne et al., 2016; Charlier et al., 2016). However, in contrast to the scarce number of studies that have examined lower extremity muscle power in pwMS, several studies have done so in aging, providing clear evidence for marked age-related decrements in muscle power exceeding that observed in muscle strength (Byrne et al., 2016; Bassey et al., 1992; Clemenson et al., 2008; Suetta et al., 2019). Moreover, lower extremity muscle power is stronger associated with physical function than muscle strength alone (Suetta et al., 2019; Bean et al., 2003; Cuoco et al., 2004; Foldvari et al., 2000; Reid and Fielding, 2012; Skelton et al., 1994). This provides a strong rationale for investigating the association between lower extremity muscle power and physical function in pwMS.

Among the many methods being used to assess lower extremity muscle power, several reasonably inexpensive, portable, and easy-to-apply devices have recently become available. One of these is the ‘draw-wire’ linear encoder, which has been primarily applied to assess muscle power during both non-weight-bearing (e.g. leg press or knee extension with the wire attached to the exercise machines’ weight stack (Alcazar et al., 2017; Medina-Perez et al., 2016)) and weight-bearing activities (e.g. chair rise with wire attached to participants’ waist (Glen et al., 2017; Lindemann et al., 2015)). The former can be interpreted as an outcome measure that reflect ‘true absolute’ maximal lower extremity muscle power, whereas the latter can be interpreted as an outcome measure that reflect ‘functional’ maximal lower extremity muscle power (i.e. taking into account the external ‘body weight’ resistance, that has to be overcome during movement alongside the complexity of the movement). This distinction is important as any potential association with physical function may differ depending on the applied approach. By using both approaches (i.e. non-weight-bearing and weight-bearing assessment) in the same study, it can help advance our understanding of muscle power.

While the evidence outlined above provide preliminary insight into the separate and somewhat analogous deleterious effects of MS and aging on lower extremity muscle power and physical function, the presently unaddressed combined effects will most likely be exacerbated (i.e. preferential muscle power reductions in pwMS with advanced age). Since decrements in lower extremity physical function (e.g. walking capacity) are more pronounced and likely even accelerated with advanced age (>60 years) in pwMS compared to HC (Hvid et al., 2020; Minden et al., 2004; Roy et al., 2017), it is plausible that lower extremity muscle power is a critical determinant.

Therefore, the aims of this exploratory cross-sectional study were to investigate how lower extremity muscle power (using a linear encoder during non-weight-bearing and weight-bearing activities) is 1) affected by aging in pwMS vs. HC (along with MS phenotypes and disease severity in pwMS), and 2) associated with lower extremity physical function (weight-bearing activities comprising short distance walking and chair rise). We hypothesized that decrements in lower extremity muscle power would 1) be present in pwMS vs. HC, 2) become more pronounced in pwMS vs. HC with advanced age, 3) become more pronounced with a shift in MS phenotypes (from relapse-remitting to progressive MS) and with increasing disease severity, and 4) be associated with decrements in lower extremity physical function in both pwMS and HC (weight-bearing lower extremity muscle power in particular).

2. Methods

2.1. Study design

The present exploratory study contains novel cross-sectional data examining the combined effects of aging and MS on lower extremity muscle power and physical function. The study was carried out from August 2018 to March 2020. Although very little data on muscle power in pwMS existed in advance of the present study, we used the previous study findings by Chung and colleagues (Chung et al., 2008) comparing lower extremity muscle power in pwMS vs. HC (85.3 ± 26.5 W vs. 109.0 ± 28.3 W; combination of knee extensor and dorsal flexor muscle power) for sample size calculation. By using a significance level of p < 0.01 and a power = 90%, n = 42 participants were deemed necessary across both pwMS and HC, corresponding to a total of n = 84. All additional subgroup analyses were deemed explorative. The study was approved by the ethics committee of Region Midtjylland, Denmark (project id: 1-10-72-206-17) and was performed in accordance with the Declaration of Helsinki. The Danish Data Protection Agency oversaw the study.

2.2. Participants

We aimed to enroll adult participants across three different age groups: young (age ≤ 44 years), middle-aged (age 45–59 years), and old (>60 years) (Table 1). A total of 42 interested and eligible pwMS were recruited from the Danish MS Hospital in Ry, Denmark. A total of 50 HC were recruited from a local senior center (offering social and cultural activities) and via the network (i.e. family, friends, colleagues) of the participating pwMS as well as the employees at Exercise Biology, Department of Public Health, Aarhus University, Denmark. Participants were included if they were 18 years or older, had preserved walking capacity (assistive devices allowed if ≤ 20 m walk distance could not be completed), and were able to independently attend the test session. Participants were excluded if they had any serious medical comorbidities affecting participation, had a blood pressure >160/100 mmHg on the day of testing, or had participated regularly (>3 sessions per week, ≥30-minute sessions) in moderate-to-high intensity structured exercise during the past 6 months. Of note, 1 male HC was excluded and omitted from further analysis, as he regularly participated moderate-to-high intensity structured exercise (>5 sessions per week, ≥60 min sessions). Therefore, a total of 42 pwMS and 49 HC were included in the analysis of the study. Standard characteristics (sex, age, height, weight) were assessed in both pwMS and HC. Self-reported disease characteristics (MS phenotype, time since diagnosis, receiving disease modifying treatments (DMT) or not) and disease severity (Patient-Determined Disease-Steps (PDDS) scale ranging from 0 to 8 where higher scores represent greater global neurological impairments primarily related to walking capacity (Hohol et al., 1995)) were assessed in pwMS only.

2.3. Assessment of lower extremity physical function

Walking capacity was measured by the timed 25-foot-walk-test (T25FWT; corresponding to 7.62 m), with participants being
2.4. Assessment of lower extremity muscle power

A linear encoder (CRONOJUMP, Bosco system, v1.8.1, Spain; sampling rate 1000 Hz) which is essentially a position transducer was used to measure muscle power during 1 x maximal chair rise (termed PowerChairRise) and 1 x maximal leg press movement (termed PowerLegPressPeak) respectively (Medina-Perez et al., 2016; Lindemann et al., 2015; Alcazar et al., 2018). The peak power parameter was calculated using a built-in software, based on the respective characteristics of the participant (height, weight) as well as the external load for the non-weight bearing test.

During the 1 x maximal chair rise, the linear encoder was fixed to the floor next to the test-chair and attached to the participant’s hip with a belt (Fig. 1A). Following standardized instructions, demonstration, and warm-up (comprising the chair rise capacity test described above), participants were instructed to cross their arms across the chest, and to rise from the chair as fast and powerful as possible completely extending the knees and hip joints (i.e. involving the ascending/concentric phase only). The test was initiated with a countdown of “3-2-1-go”. The test was performed twice interspersed by 2 min, with the better of the two results being selected for further analysis.

During the 1 x maximal bilateral leg press (Selection 700, Tecnogym, Italy; 15 degrees horizontally inclined leg press machine) the linear encoder was aligned with the placement of the feet on the leg press machine, with the wire connected to the participant’s hips with a belt (Fig. 1B). Following instructions, demonstration, warm-up (10 repetitions with an intensity corresponding to 50% body weight), and familiarization (2–3 submaximal trials), 1-repetition maximum (1-RM) was assessed (defined as the maximal load moved one time by the participant using proper technique with sufficient range of motion). Of note, 1-RM is considered the golden standard for estimation of maximal strength in non-laboratory settings (Levinger et al., 2009; Seo et al., 2012; Barbalho et al., 2018). Participants were instructed and assisted to fully extend the hip and knee joints without knee hyperextension. The movement was preceded by a slow controlled eccentric phase until the participant achieved 90 degrees of knee flexion followed by a concentric phase now performed without assistance, until achieving the starting position. 

The test was performed twice interspersed by 2 min, with the better of the two results being selected for further analysis.
were instructed to perform the concentric phase of the leg press as quickly and powerful as possible at each load intensity, with each 70% and 80% being calculated from the 1-RM load (100%). Participants of 1-RM reached within 4 min. Also, standardized verbal encouragement was given to ensure comparability across individuals; presented as W.kg⁻¹.

Fig. 1. Linear encoder placement and the wire connection to the belt on the participant’s hip during A) chair rise test and B) leg press test. The full yellow arrows indicate the placement of the linear encoder equipment, and the yellow dashed arrows indicate the wire connection to the belt. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

position. The load was progressively raised until reaching the intensity of 1-RM reached within 4–6 attempts, with each attempt interspersed by 2 min. Also, standardized verbal encouragement was given to ensure maximal effort. The percentage loads corresponding to 40%, 50%, 60%, 70% and 80% were calculated from the 1-RM load (100%). Participants were instructed to perform the concentric phase of the leg press as quickly and powerful as possible at each load intensity, with each attempt interspersed by 2 min. For each participant, we used the relative lower extremity muscle power (PowerLegPress) values to derive the highest value (PowerLegPressPeak).

2.5. Statistics

Statistics were performed using linear mixed model (STATA, IC 14, StataCorp, College Station, TX, USA). Data on all participant characteristics, muscle power measures (normalized to bodyweight to facilitate comparability across individuals; presented as W.kg⁻¹), and lower extremity physical function measures (when presented as speed) followed a normal distribution. Hence, T25FWT and 5STS are presented as meters walked per second (m.s⁻¹) and number of STS performed per second (STS.s⁻¹). In addition to separating pwMS and HC participants across age groups, pwMS were also separated according to MS phenotype (relapsing-remitting: RR and secondary-progressive: SP + PP) and self-reported disease severity (pwMS scoring ≤3: PDDS≤3 and pwMS scoring >3: PDDS>3). Participant id was set as a random effect, whereas age (young, middle-aged, old) and group (HC, MS, RR, SP + PP; PDDS≤3, PDDS>3) were set as fixed effects. In addition to age×group interactions, any potential age effect (separately in pwMS and HC) and group effect (separately in young, middle-aged, and old) were examined. Also, any potential MS phenotype effect (separately in pwMS) and self-reported disease severity effect (separately in pwMS) were examined. Regarding the main analyses of lower extremity muscle power and physical function, no adjustments were made for confounding variables (sex, education, lifestyle factors, etc.) as our sample size was deemed too small to allow this. To compare proportions of sex and assistive device users in pwMS and HC along with MS phenotypes and DMT in pwMS alone, Fisher's exact test was used. To examine associations between muscle power and physical function, simple linear regression was performed with determination coefficients (r²) being reported. To illustrate the differences between pwMS and HC, the differences between young, middle-aged, and old participants, as well as the differences between RR and SP + PP as well as PDDS≤3 and PDDS>3, percentage deficits were calculated. This was calculated as individual values for the ‘inferior’ group expressed in relation to the mean of the ‘superior’ group (i.e. pwMS vs. HC, SP + PP vs. RR, and PDDS≤3 vs. PDDS>3). Data are presented as mean ± sd in tables and as mean ± 95%CI in figures. Statistical significance level was set at p < 0.01 and denoted by the following symbols: a: different from HC (all and within age groups), b: different from young (within group), c: different from middle-aged (within group), d: different from RR (when compared to SP + PP) or PDDS≤3 (when compared to PDDS>3). This statistical significance level was chosen to reduce the risk of type I errors. Figures were made in GraphPad Prism 7.0 (GraphPad Software, La Jolla, CA, USA, www.graphpad.com).

3. Results

Participant characteristics of HC and pwMS are shown in Table 1. Overall, no differences were observed between HC and pwMS in terms of male to female ratio, age, body height, and BMI. In pwMS, an age effect (p < 0.01) was observed for all disease characteristics in pwMS, i.e. with longer time since diagnosis in old vs. young, higher prevalence of progressive (and vice versa, lower prevalence of relapsing-remitting) MS phenotype in old vs. young, higher PDDS score in old vs. middle-aged and in old vs. young, fewer receiving DMT in old vs young, along with higher prevalence of using assistive devices in old vs. middle-aged and in old vs. young.

Advanced age was inversely associated with lower extremity muscle power in all pwMS and in all HC (Fig. 2A–B). Slope steepness of PowerLegPressPeak was almost identical in pwMS and HC (corresponding to declines of −0.40 vs. −0.42 W.kg⁻¹ per decade, respectively; Fig. 2A). While no difference was observed, visual inspection suggested that slope steepness of PowerChairRise was greater in pwMS vs. HC (corresponding to declines of −2.53 vs. −2.03 W.kg⁻¹ per decade, respectively; Fig. 2B).

PowerLegPressPeak and PowerChairRise were reduced in all pwMS vs. HC (deficits of −23% and −26%, respectively; p < 0.01) as well as in young (PowerChairRise only: −17%, p < 0.05), middle-aged (−37% and −37%, respectively; p < 0.01), and old (PowerChairRise only: −27%, p < 0.01) (Table 2, Fig. 3A–B). While no group×age interactions were observed, the pattern of changes appeared to be largest from young to middle-aged in pwMS, and from middle-aged to old in HC (supported by the largest deficits observed in middle-aged pwMS). Moreover, deficits in PowerLegPressPeak and PowerChairRise were observed in SP + PP vs. RR (−26% and −19%, respectively; p < 0.01) and in PDDS≥3 vs. PDDS>3 (−32% and −36%, respectively; p < 0.01) (Table 3, Fig. 3A–B). Individual PowerLegPressPeak derived from the relative PowerLegPress values was predominantly observed at 60% or 70% of 1RM in pwMS, and at 50%, 60%, or 70% of 1RM in HC (Supplementary Fig. 1, Supplementary Table 1). All relative PowerLegPress values across the different relative loadings of 1RM (except for 100% of 1RM) were reduced in pwMS vs. HC (p < 0.01). SP + PP vs. RR (p < 0.01), and PDDS≥3 vs. PDDS>3 (p < 0.01) (Supplementary Fig. 1, Supplementary Table 1).

T25FWT and 5STS were also reduced in all pwMS vs. HC (deficits of
Fig. 2. Associations between age and lower extremity muscle power (A: normalized PowerLegPressPeak in W kg⁻¹; B: normalized PowerChairRise in W kg⁻¹) across HC (n = 49) and pwMS (n = 42). Simple linear regression analyses were performed, with determination coefficients (r²), p-value, and slope steepness being displayed. Slope steepness correspond to reductions in lower extremity muscle power per decade.

Table 2
Lower extremity muscle power and physical function in HC and pwMS – effect of aging.

|                      | All          | Young        | Middle-aged | Old          |
|----------------------|--------------|--------------|-------------|--------------|
| PowerLegPressPeak (W·kg⁻¹) |              |              |             |              |
| HC*                  | 2.89 ± 1.28  | 3.71 ± 1.54  | 3.12 ± 0.86 | 2.25 ± 1.09  |
| pwMS*                | 2.24 ± 1.02  | 2.98 ± 1.15  | 1.99 ± 0.73 | 1.89 ± 0.89  |
| PowerChairRise (W·kg⁻¹) |              |              |             |              |
| HC*                  | 15.62 ± 4.65 | 19.59 ± 4.15 | 17.45 ± 3.49| 11.95 ± 2.90 |
| pwMS*                | 11.50 ± 4.54 | 15.78 ± 4.58 | 10.94 ± 3.27| 8.65 ± 2.90  |
| T25FWT (m·s⁻¹)   |              |              |             |              |
| HC*                  | 2.22 ± 0.36  | 2.43 ± 0.36  | 2.46 ± 0.24 | 1.95 ± 0.23  |
| pwMS*                | 1.50 ± 0.57  | 1.85 ± 0.52  | 1.62 ± 0.41 | 1.07 ± 0.49  |
| 5STS (STS·s⁻¹)      |              |              |             |              |
| HC*                  | 3.50 ± 0.59  | 3.19 ± 0.41  | 3.12 ± 0.30 | 3.97 ± 0.51  |
| pwMS*                | 6.41 ± 4.17  | 4.97 ± 3.57  | 5.00 ± 1.32 | 9.05 ± 5.31  |
| 5STS (s)            |              |              |             |              |
| HC*                  | 0.86 ± 0.17  | 0.99 ± 0.15  | 0.89 ± 0.12 | 0.76 ± 0.17  |
| pwMS*                | 0.64 ± 0.23  | 0.84 ± 0.18  | 0.64 ± 0.20 | 0.48 ± 0.16  |

PowerLegPressPeak: normalized muscle power derived from leg press, PowerChairRise: normalized muscle power derived from chair rise, T25FWT: timed 25 foot-walk test, 5STS: 5 times sit-to-stand, HC: healthy controls, pwMS: persons with multiple sclerosis. Values are presented as mean ± SD. *: age effect (within group), a: different from HC (all and within age groups), b: different from young (within group), c: different from middle-aged (within group). Statistical significance level was set at p < 0.01. See Fig. 3 for individual data points along with deficits between pwMS and HC. Displayed in grey text, T25FWT and 5STS are also reported as absolute values (s) to enable comparison with previous study reports. PowerLegPressPeak are derived from individual peak values of normalized PowerLegPress (W·kg⁻¹) at relative loadings of 40–80% and 100% 1RM (see Supplementary Fig. 1 and Supplementary Table 1 for further information).
lower extremity muscle power concomitant with lower extremity physical function across the lifespan in pwMS, thereby emphasizing the combination of MS and aging. In accordance with our study aims, the main findings were that decrements in lower extremity muscle power 1) were greater in pwMS vs. HC (supporting our hypothesis; robust according to the study sample size), 2) did not become more pronounced in pwMS vs. HC with advanced age (contrasting our hypothesis), although the pattern of changes appeared to be more evident from young to middle-aged in pwMS and from middle-aged to old in HC (supported by the largest deficits observed in middle-aged), 3) decrements in lower extremity muscle power in pwMS became more pronounced with a shift in MS phenotype (from RR to SP + PP) as well as increasing disease severity.

**Table 3**

| Participants (n) | RR | SP+PP | PDDS0–3 | PDDS4–7 |
|-----------------|----|-------|---------|---------|
| PowerLegPressPeak (W kg⁻¹) | 2.61 ± 1.12 | 1.93 ± 0.83 | 2.60 ± 1.03 | 1.76 ± 0.80 |
| PowerChairRise (W kg⁻¹) | 12.82 ± 4.99 | 10.41 ± 3.91 | 13.63 ± 4.19 | 8.67 ± 3.32 |
| T25FWT (m s⁻¹) | 1.74 ± 0.52 | 1.30 ± 0.54 | 1.87 ± 0.33 | 0.94 ± 0.36 |
| T25FWT (s) | 4.86 ± 1.78 | 7.68 ± 5.10 | 4.22 ± 0.85 | 9.69 ± 5.01 |
| SSTS (STS s⁻¹) | 0.71 ± 0.22 | 0.58 ± 0.23 | 0.77 ± 0.18 | 0.47 ± 0.17 |
| SSTS (s) | 7.99 ± 3.67 | 10.63 ± 6.68 | 6.83 ± 1.70 | 12.92 ± 7.06 |

**PowerLegPressPeak**: normalized muscle power derived from leg press, **PowerChairRise**: normalized muscle power derived from chair rise, T25FWT: timed 25 foot-walk test, SSTS: 5 x sit-to-stand, pwMS: persons with multiple sclerosis, RR: relapsing-remitting, SP: secondary progressive, PP: primary progressive, PDDS: patient determined disease steps. Values are presented as mean ± SD. d: different from RR (when compared to SP + PP) or PDDS0–3 (when compared to PDDS4–7). Statistical significance level was set at p < 0.01. See Fig. 3 for individual data points along with deficits between pwMS and HC. Displayed in grey text, T25FWT and SSTS are also reported as absolute values (s) to enable comparison with previous study reports.

Fig. 3. Lower extremity muscle power (A: normalized PowerLegPressPeak in W kg⁻¹; B: normalized PowerChairRise in W kg⁻¹) and lower extremity physical function (C: T25FWT in m s⁻¹; D: SSTS in STS s⁻¹) in all (HC (n = 49), pwMS (n = 42)) as well as in age groups (young, middle-aged, old), MS phenotype groups (RR, SP + PP), and MS disease severity groups (PDDS0–3, PDDS4–7). Percentage deficits between ‘inferior’ and ‘superior’ groups (i.e., pwMS vs. HC, SP + PP vs. RR, and PDDS4–7 vs. PDDS0–3) are also displayed. Data are presented as mean ± CI99% accompanied by individual values. For further details, see Tables 2 and 3.
Table 4
Associations between lower extremity muscle power and lower extremity physical function.

|                | PowerLegPressPeak - T25FWT | PowerChairRise - T25FWT | PowerLegPressPeak - 5STS | PowerChairRise - 5STS |
|----------------|-----------------------------|--------------------------|--------------------------|------------------------|
|                | (n) | r²-value | p-value | r²-value | p-value | r²-value | p-value | r²-value | p-value |
| HC             | 49  | 0.23     | <0.01   | 0.39     | <0.01   | 0.18     | <0.01   | 0.27     | <0.01   |
| Young          | 12  | 0.05     | 0.466   | 0.15     | 0.209   | 0.02     | 0.631   | 0.08     | 0.366   |
| Middle-aged    | 16  | 0.01     | 0.771   | 0.01     | 0.768   | 0.05     | 0.429   | 0.03     | 0.551   |
| Old            | 21  | 0.24     | 0.024   | 0.18     | 0.058   | 0.20     | 0.040   | 0.23     | 0.028   |
| pwMS           | 42  | 0.45     | <0.01   | 0.53     | <0.01   | 0.50     | <0.01   | 0.61     | <0.01   |
| Young          | 12  | 0.65     | <0.01   | 0.42     | 0.022   | 0.42     | 0.022   | 0.28     | 0.079   |
| Middle-aged    | 15  | 0.13     | 0.215   | 0.29     | 0.046   | 0.44     | <0.01   | 0.48     | <0.01   |
| Old            | 15  | 0.38     | 0.018   | 0.42     | 0.012   | 0.42     | <0.01   | 0.58     | <0.01   |
| RR             | 23  | 0.33     | 0.013   | 0.43     | <0.01   | 0.46     | <0.01   | 0.52     | <0.01   |
| SP+PP          | 19  | 0.50     | <0.01   | 0.56     | <0.01   | 0.49     | <0.01   | 0.67     | <0.01   |
| PDDS0–3        | 24  | 0.41     | <0.01   | 0.39     | <0.01   | 0.44     | <0.01   | 0.37     | <0.01   |
| PDDS4–7        | 18  | 0.47     | <0.01   | 0.47     | <0.01   | 0.36     | <0.01   | 0.61     | <0.01   |

PowerLegPressPeak: normalized muscle power derived from leg press (W kg⁻¹), PowerChairRise: normalized muscle power derived from chair rise (W kg⁻¹), T25FWT: timed 25 foot-walk test (m s⁻¹), 5STS: 5 times sit-to-stand (STS s⁻¹), HC: healthy controls, pwMS: persons with multiple sclerosis, RR: relapsing-remitting, SP: secondary progressive, PP: primary progressive, PDDS: patient determined disease steps (PDDS 0–3: pwMS scoring <4, PDDS4–8: pwMS scoring ≥4). Associations between lower extremity muscle power and lower extremity physical function are displayed as determination coefficients (r²) and exact p-values for HC and pwMS (all and within age groups), with the statistical significance level set at p < 0.01. Non-significant associations are shown in grey text. See Fig. 4 for visualization of associations in pwMS (including individual data points).

Fig. 4. Associations between lower extremity muscle power and lower extremity physical function (A: normalized PowerLegPressPeak in W kg⁻¹ and T25FWT in m s⁻¹; B: normalized PowerChairRise in W kg⁻¹ and T25FWT in m s⁻¹; C: normalized PowerLegPressPeak in W kg⁻¹ and 5STS in STS s⁻¹; D: normalized PowerChairRise in W kg⁻¹ and 5STS in STS s⁻¹) as well as between disease severity and lower extremity muscle power (E: PDDS score and normalized PowerLegPressPeak in W kg⁻¹; F: PDDS score and normalized PowerChairRise in W kg⁻¹) across pwMS (n = 42). Simple linear regression analyses were performed, with determination coefficients (r²), p-value, and slope steepness being displayed. Slope steepness correspond to changes on y-axis when x-axis changes by a unit of 1. For further details, see Table 4.
severity (from PDDS0–3 to PDDS4+) (supporting our hypothesis), and 4) were strongly associated with lower extremity physical function (explaining 45% to 61% of T25FW and 5STS) and disease severity (PDDS explained 31% to 38% of lower extremity muscle power) (supporting our hypothesis).

The present study findings verify that lower extremity neuromuscular function is reduced in pwMS vs. HC (total sample and all age groups, respectively), as evidenced by numerous studies reporting data on lower extremity muscle strength (i.e. isometric, dynamic, and explosive muscle strength) (Jorgensen et al., 2017; Scott et al., 2011; Sieljacks et al., 2020; Cruz et al., 2019) along with one study reporting data on lower extremity muscle power (Chung et al., 2008). In the latter study by Chung and colleagues involving pwMS aged 55 ± 9 years (i.e. comparable to the total sample of pwMS in the present study), muscle power was assessed during isometric muscle contractions at 45% of maximal isometric strength (Chung et al., 2008), thus resembling our assessment of PowerLegPress at 40% to 50% of 1RM. The major difference is that Chung and colleagues examined isolated muscle groups (knee extensor and dorsal flexor), whereas we examined multiple muscle groups involved during leg press (primary knee extensor, knee flexor and hip extensor). Interestingly, Chung and colleagues did not observe any substantial deficit in dorsal flexor muscle power in pwMS vs. HC (−8%) whereas the deficit in knee extensor muscle power (−23%) was more pronounced (Chung et al., 2008), thus resembling the deficit we observed during PowerLegPress at 40% to 50% of 1RM (−27%; Supplementary Table 1, Supplementary Fig. 1). These observations are aligned with, and may be partly explained by, the fact that certain muscle groups are preferentially involved in weight-bearing propulsive activities such as walking and thus relying on power generation (e.g. knee extensor and plantar flexor (Sieljacks et al., 2020; Manago et al., 2018)), whereas other muscle groups are not or at least to a much smaller extent (e.g. dorsal flexor). While we can only speculate whether specific muscle groups are more susceptible towards MS, future studies are warranted to verify this notion.

With advanced age, lower extremity muscle power became reduced to a comparable extent in pwMS and HC. However, an interesting distinction was observed between the two approaches used to assess maximal lower extremity muscle power. It appeared that PowerChairRise (i.e. weight-bearing lower extremity muscle power) were affected to a greater extent than PowerLegPress (i.e. non-weight-bearing lower extremity muscle power), as supported by the numerically greater decrement in PowerChairRise in pwMS vs. HC (−2.53 vs. −2.03 W·kg⁻¹ per decade, respectively) but not in PowerLegPress (−0.40 vs. −0.42 W·kg⁻¹ per decade, respectively) (Fig. 2A–B), alongside the somewhat greater deficit in old pwMS in PowerChairRise vs. PowerLegPress (−27% vs. −16%, respectively) (Fig. 3A–B). As we argue in the introduction, PowerLegPress can be interpreted as an outcome measure that reflect ‘true absolute’ maximal lower extremity muscle power (i.e. intrinsic power generating capacity of the lower extremity muscles) involving a movement of low complexity. In a previous study from our group (Sieljacks et al., 2020), we observed age- and MS-related alterations in knee extensor isometric and dynamic concentric muscle strength that were somewhat similar to that observed in PowerLegPressPeak in the present study. It is thus plausible that PowerChairRise – which we argue can be interpreted as an outcome measure that reflect ‘functional’ maximal lower extremity muscle power involving a movement of high complexity, and thus not relying on the intrinsic power generating capacity of the lower extremity muscles alone – are preferentially affected with aging and MS. In support hereof, recent studies have reported a pronounced and even accelerated loss of physical function (walking capacity in particular) with advanced age in pwMS compared to HC (Sieljacks et al., 2020; Hvid et al., 2020; Roy et al., 2017). Altogether, the different methods available to assess lower extremity muscle power appear to yield context-dependent and different results requiring careful interpretation.

Lower extremity muscle power also became more reduced with an increase in disease severity (along with a shift in MS phenotype from RR to SP + PP), as evidenced by the associations between PDDS and lower extremity muscle power deficits (Fig. 4E–F). In a previous review from our group, we provided somewhat similar evidence that EDSS (Expanded Disability Status Scale) was associated with lower extremity muscle strength deficits (Jorgensen et al., 2017). These findings altogether suggest that substantial decrements in lower extremity neuromuscular function are a hallmark of MS, representing useful outcomes reflecting the disease-related neurodegenerative consequences of MS (Lassmann, 2013; Vucic et al., 2010; Mamoei et al., 2020). This will most likely become more pronounced in old pwMS due to the biological process of aging that are also accompanied by neurodegenerative consequences (Borzuola et al., 2020; Hepple and Rice, 2016). In comparison to HC, several studies including pwMS have reported preferential structural and functional changes of the brain and nervous system, including brain atrophy of whole/regional brain related to motor function (Locca et al., 2017), impaired central motor conduction, loss of neurons and motor units, and reduced neural activation of the muscles (relying on recruitment and firing rates of motor units) (Mamoee et al., 2020). Also, a few studies have reported preferential muscle atrophy (especially of type II fibers, a main mechanism responsible for high intrinsic power generating capacity) and reduced muscle quality (e.g. increased muscular fat infiltration, reduced single muscle fiber contractility) (Garner and Widrick, 2003; Wens et al., 2014). While these changes within the brain, nervous system, and skeletal muscle are likely responsible for the observed decrements in lower extremity muscle power, we cannot tease out how they separately change when going from young to middle-aged to old. Moreover, all of these changes are likely modified by lifestyle factors such as physical activity, well-known to be associated with lower extremity neuromuscular function in pwMS (Rooney et al., 2019), and well-known to be substantially reduced in pwMS compared to HC (Casey et al., 2018). Yet, these notions are purely speculative as we did not assess any of these 'tissue specific' adaptations or the levels of physical activity in the present study.

To elaborate on the differences between the two methods we used to assess lower extremity muscle power, PowerChairRise showed four- to five-fold higher values compared to PowerLegPressPeak despite that both were derived from related multi-joint movement tasks. In part, this can be explained by the fact that chair rise preferentially involves movement of the upper body (e.g. back extension) and thus more muscle groups contribute to the power production. Lindemann and colleagues observed somewhat comparable findings when they examined power values derived from chair rise vs. bilateral leg extension (Nottingham Power Rig) in older HC (Lindemann et al., 2016). The observed values of lower extremity muscle power were of the same magnitude as previously reported when using the same methodological approaches, both in young to middle-aged pwMS (Medina-Perez et al., 2016), and in old HC (Alcazar et al., 2017; Glenn et al., 2017; Lindemann et al., 2015).

Although no previous studies have examined whether lower extremity muscle power is associated with physical function in pwMS, the observed strong associations (explaining 45% to 61%, Fig. 4A–D) exceed or at least parallel what has previously been reported between lower extremity muscle strength and physical function in pwMS (review study: explaining 20% to 30% (Ramari et al., 2020); original study involving young, middle-aged and old pwMS: explaining 21% to 61% (Sieljacks et al., 2020)). This notion seems aligned with the aging studies that have directly compared and shown that lower extremity muscle power is stronger associated with physical function strength alone (Bean et al., 2003; Cuoco et al., 2004; Foldvari et al., 2000; Skelton et al., 1994). To gain further insight, we examined how lower extremity muscle strength (which could also be derived from the chair rise and leg press test) were associated with 5STS and T25FWT in pwMS. Interestingly, while 5STS were similarly associated with muscle power and muscle strength (chair rise: $r^2 = 0.57$ vs. $r^2 = 0.61$, respectively; leg press: $r^2 = 0.48$ vs. $r^2 = 0.50$), T25FWT appeared to be slightly stronger associated with muscle power compared to muscle strength (chair rise: $r^2$...
r^2 = 0.53 vs. r^2 = 0.43, respectively; leg press: r^2 = 0.45 vs. r^2 = 0.31) (data not shown). In continuation of the above-mentioned discussion of decrements in lower extremity neuromuscular function being a hallmark of MS, these findings suggest that lower extremity muscle power (compared to muscle strength) represent a useful outcome reflecting the neurodegenerative disease-related consequences of MS. Although the present findings on ‘linear encoder derived’ lower extremity muscle power were not put into context of any thresholds of clinical significance (as no such thresholds currently exist), future studies should help establish these.

The findings of the present explorative study are nevertheless still of clinical importance. Almost one-third of all pwMS are 60 years or older (Mackenzie et al., 2014; Magyari and Sorensen, 2019; Wallin et al., 2019), a number that is expected to increase during the coming decades (Amankwa et al., 2017). The present study as well as recent studies have reported a pronounced and even accelerated loss of walking capacity - accompanied by an increased prevalence of dismobility and frailty - with advanced age in pwMS compared to HC (Sieljacks et al., 2020; Hvid et al., 2020; Roy et al., 2017; Ayrignac et al., 2020). As the present novel study findings suggest lower extremity muscle power to be a critical determinant of lower extremity physical function, we strongly recommend that preventive/rehabilitative strategies for pwMS (old individuals in particular) also aim at improving lower extremity muscle power. To achieve this, high-intensity power training (i.e. resistance training emphasizing moderate-to-high loading at maximal intended movement velocity) has been proven highly effective in young/middle-aged pwMS (Medina-Perez et al., 2016) and in old HC (Marsh et al., 2009; Reid et al., 2015).

A number of methodological considerations of the present explorative study deserve mentioning. The main strengths are 1) the enrolment of both pwMS and HC across the adult lifespan, enabling us to tease out the deleterious effects of MS vs. advanced age (i.e. presenting a realistic scenario that is expected in pwMS), along with 2) the novel and extensive assessment of lower extremity muscle power along with the link to lower extremity physical function. The main limitations are 1) cross-sectional study design which contain aspects that potentially could have affected the results and interpretation such as inferring longitudinal/prospective changes by comparing different age groups as well as the comparison of two groups having different life expectancy (6–10 years shorter in pwMS vs HC (Lunde et al., 2017; Scalfari et al., 2011)) (discussed in detail elsewhere (Hvid et al., 2020)), 2) the study sample size appeared insufficient for the comparisons across the different subgroups (age groups, MS phenotype groups, disease severity groups), which along with the multiple comparisons increased the risk of type 1 errors (despite our attempt to reduce this by using a significance level of p < 0.01), 3) the enrolment of pwMS having preserved walking capacity without/with assistive devices (i.e. EDSS score ≤ 6.5) only, which may lead to recruitment of a ‘functionally better’ sample of pwMS (old in particular), and 4) the observed decrements of muscle power and physical function (walking and chair rise capacity) could not be interpreted in relation to any thresholds of clinical significance (as no such thresholds currently exist). Overall, these study limitations may affect the external/ecological validity of the study findings and must be taken into account when interpreting the study findings.

5. Conclusions

The combined effects of MS and aging reveal substantial decrements in lower extremity muscle power that is accompanied by (and strongly associated with) decrements in lower extremity physical function. While these decrements in muscle power did not appear to become more pronounced in pwMS vs. HC with advanced age, the pattern of changes differed between pwMS (most evident early in the lifespan, from young to middle-aged) and HC (most evident later in the lifespan, from middle-aged to old). Furthermore, decrements in lower extremity muscle power became more pronounced with a shift in MS phenotype and disease severity. We propose that lower extremity muscle power should be viewed as a clinically important factor (i.e. a critical determinant of lower extremity physical function) in pwMS, which should be specifically targeted by preventive and rehabilitative exercise strategies and perhaps also used as a screening tool for early neuromuscular deterioration.

CRediT authorship contribution statement

Conceptualization: UD, LGH, AGS; data collection and analysis: RAWS, CR, AGS, CT, LGH; writing – original draft: RAWS, CR, LGH; writing – revision and editing: RAWS, CR, AGS, CT, UD, LGH.

Declaration of competing interest

None of the authors have any declaration of interests

Acknowledgements

We like to thank all study participants for their interest and essential involvement in the study.

Funding

The study received no funding.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2021.111347.

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