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Oxygen Cost of Walking and Its Correlates in Multiple Sclerosis

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OXYGEN COST OF WALKING AND ITS CORRELATES IN MULTIPLE SCLEROSIS

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ABSTRACT

Multiple sclerosis (MS) is a chronic, neurological disease characterized by demyelination and transection of axons as well as loss of neurons in the central nervous system that may result in poor walking efficiency, indicated by an increase in the oxygen cost of walking (C_w). The C_w is defined as the amount of oxygen consumed per kilogram of body weight per unit distance walked and reflects disability-related gait abnormalities and manifestations and its interaction with the environment. This dissertation involved four research projects. The first project provided an overview of existing research on the C_w in MS and established a research agenda directed toward better understanding the factors related to the C_w in persons with MS. The second project examined objective measures of fitness (i.e., aerobic capacity, muscular strength, and postural control) as putative modifiable variables associated with the C_w in adults with MS who had moderate disability. The third project examined the associations among C_w, spasticity of the ankle plantarflexors, and spatiotemporal gait parameters in persons with MS who had moderate disability. The last project examined the relationship among C_w, body composition metrics, and disease-related outcomes among persons with MS with a wide distribution of body composition profiles. Collectively, this line of research provided critical information on the C_w and its correlates and potential consequences in MS, and the findings may guide the design and development of targeted approaches for managing the C_w and its secondary consequences in MS such as disability and physical well-being.

Keywords: multiple sclerosis; energy expenditure; fitness; spasticity; gait; body composition

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INTRODUCTION

Multiple sclerosis (MS) is a chronic, neurological disease characterized by demyelination and transection of axons as well as loss of neurons in the central nervous system[1] that may result in poor walking efficiency, indicated by an increase in oxygen cost of walking (C_w).[2, 3] C_w is defined as the amount of oxygen consumed per kilogram of body weight per unit distance walked, and reflects contributions of disability-related gait abnormalities and manifestations and the interaction with the environment.[3] Conceptually, C_w can increase as a function of shorter distance traveled while expending the same amount of energy, or as a function of greater energy expenditure for the same distance traveled. Those with higher C_w likely have diminished capacity for everyday life challenges based on a reduction in aerobic reserve necessary to meet the energy demands required of daily life. There is preliminary evidence that the C_w is 2-3 times higher in persons with MS compared with adults of the general population.[2] Some studies have established that persons with MS who have elevated C_w demonstrated worse levels of disability status and fatigue severity as well as lower levels of daily physical activity.[4, 5] The C_w may perhaps be related to other disease-related outcomes in persons with MS such as spasticity, pain, depression, and quality of life. To that end, this dissertation involved 4 projects for better understanding C_w in MS for informing future work moving toward rehabilitation interventions for improving the energetic efficiency of walking in MS.

This first project provides an overview of existing research on the C_w and establishes a research agenda directed toward better understanding factors associated with the

C_w in persons with MS. The second project examines objective measures of fitness (i.e., aerobic capacity, muscular strength, and postural control) as modifiable correlates and predictors of C_w in adults with MS who have moderate disability. If we can identify the domains of fitness that are associated with elevated C_w in persons with moderate MS, this evidence would provide preliminary guidance for the design of exercise training interventions for reducing C_w in persons with moderate MS. The third project examines the associations among C_w, spasticity of the ankle plantarflexors, and spatiotemporal gait parameters in persons with MS who had moderate disability, as spasticity and gait dysfunction (i.e., reduced cadence, shorter step length) may possibly explain the elevated C_w in persons with moderate MS. The findings would highlight the importance of developing therapeutic, rehabilitation interventions for eventual inclusion in clinical practice for managing spasticity as an approach for reducing C_w.

Body composition may be another potential factor that influences C_w in persons with MS. Other correlates of C_w in MS may include pain, depression, anxiety, and quality of life. To date, few studies have examined the relationship among the C_w, body composition, and those disease-related outcomes in MS. To that end, the fourth project examines the relationship among the C_w, body composition metrics, and disease-related outcomes (i.e., fatigue, pain, depression, anxiety, quality of life) in persons with MS with a wide distribution of body composition profiles. This proposed line of research will provide preliminary evidence to better understand C_w and its correlates and potential consequences, and the findings may guide the design of targeted approaches for managing C_w and its consequences such as disability and quality of life in persons with MS

OXYGEN COST OF WALKING IN MULTIPLE SCLEROSIS: REVIEW AND FUTURE DIRECTIONS

by

BRENDA JENG & ROBERT W. MOTL

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INTRODUCTION

Multiple sclerosis (MS) is a chronic neurological disease characterized by immune-mediated demyelination and transection of axons as well as neurodegenerative processes involving loss of neurons within the central nervous system (CNS) [1]. The disease process results in white matter damage and grey matter atrophy in the CNS and ultimately mobility disability [2]. Walking impairment is one of the most prevalent and life-altering consequences of MS, and is often documented and tracked over time based on performance tests such as the Timed 25-Foot Walk and 6-Minute Walk (6MW) [3-5]. Such performance tests, particularly the 6MW, can further be conducted with instrumentation for measuring mechanical movement (e.g., accelerometers or gyroscopes) and/or physiological efficiency (e.g., oxygen [O_2] consumption). This is important, as walking impairment seemingly becomes more concerning when it co-occurs with an increase in energy expenditure, and this process is expressed as the energetic or O_2 cost of walking. There is long-standing interest in O_2 cost of walking as an outcome measure in MS (c.f., Olgiati), and this interest has expanded over the past decade. To that end, we provided an overview of existing research on the O_2 cost of walking in MS. This review establishes a research agenda directed toward better understanding the O_2 cost of walking and its influences and consequences in MS, and then informing interventions that may reduce O_2 cost of walking and its secondary consequences in persons with MS. We structure the review based on defining the O_2 cost of walking and its measurement. We then discuss the O_2 cost of walking in MS, including comparisons with healthy controls, its association with

other factors that represent influences and consequences, and approaches for management. We end the paper by identifying limitations of the existing research and potential directions for future examination in MS.

O_2 COST OF WALKING

Definition

Walking (i.e., bipedal movement of the body on foot through alternating and advancing footsteps) involves the sequential and rhythmical contraction of the upper and lower leg and arm musculature resulting in physiological energy expenditure (i.e. O_2 consumption). The physiological energy expenditure is necessary for locomotion or ambulatory movement and scaled based on the internal and external demands of traveling through space. The O_2 cost of walking, therefore, is defined as the amount of O_2 consumed per kilogram of body weight per unit distance traveled [6]. Conceptually, the O_2 cost of walking reflects the energy required for walking and can increase as a function of shorter distance traveled while expending the same amount of energy, or as a function of increased energy expenditure for walking the same distance. By extension, two people may walk the same distance, yet, the O_2 demand of the body may differ between them resulting in differential O_2 cost of walking (i.e., the same bout of walking is more or less energetically costly for one person than the other). This permits a quantitative assessment of the interaction between rates of O_2 consumption and walking speed/distance with values of the O_2 cost of walking that are comparable with those of the general population for understanding influences on pathological gait and gait efficiency. Collectively, the O_2 cost of walking represents a physiological marker of walking impairment that reflects the contributions of

pathological gait abnormalities and other manifestations caused by disability [6] and its interaction with external constraints.

Measurement

The study of the O_2 cost of walking requires accurate measurement of expired respiratory gases through indirect calorimetry as well as walking distance/speed; the latter component is easily measured using a distance wheel or precisely controlled on a calibrated, motor driven treadmill. Of note, some researchers have focused on the Physiological Cost Index, or the difference between resting and active heart rate, as a measure of energy efficiency during walking, yet MS may result in cardiovascular autonomic dysregulation through lesions in the brainstem (i.e., medulla or cardiovascular control center), for example, that can influence heart rate and its regulation during walking [7]. Accordingly, the O_2 cost of walking is typically measured based on O_2 consumption using a stationary telemetric metabolic cart while walking on a treadmill or a portable metabolic system while walking over-ground. Importantly, there are many metabolic systems for capturing measurements of O_2 consumption, and values for O_2 consumption may vary by device manufacturer [8]. For example, the True One 2400 (Parvo Medics, Salt Lake City, UT, USA), a telemetric metabolic cart, and the K4b^2 (COSMED, Rome, Italy), a portable metabolic system, are both systems that have been validated in healthy controls for measuring O_2 consumption, and have often been utilized in studies involving persons with MS. We utilized both a telemetric metabolic cart during treadmill walking and portable metabolic system during over-ground walking and reported comparable values in O_2 cost of walking in persons with mild MS [9]. The O_2 cost of walking on a treadmill at 80

$m \cdot m^{-}1$ was 0.179 $ml \cdot kg^{-1} \cdot m^{-1}$, and the O_2 cost of walking over-ground at 77 $m \cdot m^{-1}$ was 0.172 $ml \cdot kg^{-1} \cdot m^{-1}$ in persons with mild MS. Beyond metabolic systems, researchers must select an approach for administering walking such as over-ground or on a treadmill. The use of a treadmill precisely controls speed, and may be a good approach based on factors such as limited laboratory space. Of note, treadmill walking and over-ground walking may involve substantially different gait mechanics, and persons with walking impairments may have difficulty walking on a treadmill; this suggests that treadmill walking may not be an accurate reflection of free-living walking in persons with MS. Regarding test duration, researchers often opt for 6 minutes of walking, as it clearly allows for the achievement of steady-state O_2 consumption (VO_2) in the last 3 minutes of a 6-minute bout of walking (see Figure 1). Net steady-state VO_2, or the difference between average steady-state VO_2 and average resting-state VO_2 values, is measured as a control for influential factors such as physical activity and food intake on resting energy expenditure. The O_2 cost of walking is then expressed as $ml \cdot kg^{-1} \cdot m^{-1}$ by dividing steady-state VO_2 in $ml \cdot kg^{-1} \cdot min^{-1}$ by actual walking speed in $m \cdot min^{-1}$ (O_2 cost of walking = (steady-state VO_2 – resting VO_2) / speed).

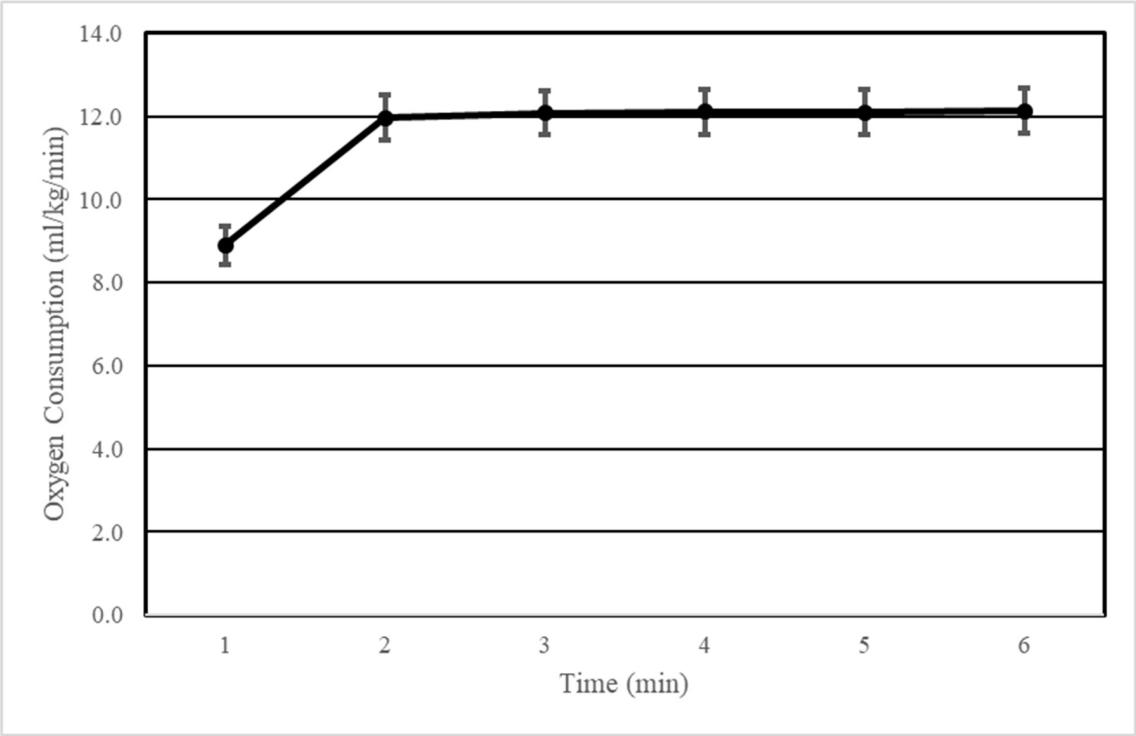

Figure 1. Oxygen consumption (VO_2) over a six-minute walk test in persons with MS. The data are from a paper involving a sample of 44 persons with MS [10].

O_2 COST IN MS

MS vs. Control

There has been interest in determining the difference in O_2 cost of walking between persons with MS and controls without MS. There is consistent evidence that persons with MS have elevated O_2 cost of walking compared with healthy controls. For example, one study reported that the O_2 cost of treadmill walking at slow speeds was between two and three times higher in persons with MS compared with controls [11]. Those with MS demonstrated mean values (standard error of the mean) for the O_2 cost of walking of 0.299 (0.019) $ml \cdot kg^{-1} \cdot m^{-1}$ at 2 $km \cdot h^{-1}$ and 0.285 (0.042) $ml \cdot kg^{-1} \cdot m^{-1}$ at 4 $km \cdot h^{-1}$, whereas controls demonstrated values of 0.147 (0.006) $ml \cdot kg^{-1} \cdot m^{-1}$ at 2 $km \cdot h^{-1}$ and 0.110 (0.005)

$ml \cdot kg^{-1} \cdot m^{-1}$ at 4 $km \cdot h^{-1}$. Similar results have been reported in another study regarding the O_2 cost of treadmill walking in persons with MS compared with controls at slow (36 $m \cdot m^{-1}$) speeds [12]. Another study extended the results of aforementioned research by measuring the difference in O_2 cost of treadmill walking at slow (54 $m \cdot m^{-1}$), moderate (80 $m \cdot m^{-1}$), and fast (107 $m \cdot m^{-1}$) speeds in persons with mild MS and healthy controls [9]. Persons with mild MS demonstrated significantly higher mean O_2 cost values (standard deviation) of 0.202 (0.023), 0.179 (0.020), and 0.190 (0.024) $ml \cdot kg^{-1} \cdot m^{-1}$ at 54, 80, and 107 $m \cdot m^{-1}$, respectively, than healthy controls with values of 0.186 (0.010), 0.163 (0.013), and 0.172 (0.011) $ml \cdot kg^{-1} \cdot m^{-1}$, respectively. Another study assessed the O_2 cost of over-ground walking and reported a significantly higher value for the O_2 cost of walking in persons with mild MS (0.19 [.05] $ml \cdot kg^{-1} \cdot m^{-1}$) compared with controls (0.17 [0.03] $ml \cdot kg^{-1} \cdot m^{-1}$) [13]. Collectively, the research supports that the O_2 cost of walking is higher across a range of conditions in persons with MS than controls, even in those with MS who have mild disability.

Disability Status

Mobility disability is a defining feature of MS that has been associated with the O_2 cost of walking. We located two studies that examined the O_2 cost of walking as a function of disability status in MS. One study measured the O_2 cost of over-ground walking across three speeds, namely comfortable (76.6 ± 13.0 $m \cdot m^{-1}$), slower (64.2 ± 12.3 $m \cdot m^{-1}$), and faster (89.0 ± 13.8 $m \cdot m^{-1}$) walking [9]. The results indicated that disability status, based on Patient Determined Disease Status (PDDS) scores, was strongly correlated with O_2 cost of walking at comfortable ($r = 0.60$), fast ($r = 0.65$), and slow ($r = 0.53$) speeds in

persons with MS. The correlations indicated that those with worse disability had a higher energetic cost of walking. Another study replicated and extended those findings among a sample of persons with MS who had a broader range of disability and reported that persons with MS who had worse disability, as indicated by the PDDS scores, demonstrated greater O_2 cost of walking ($r = 0.55$) [14]. Overall, the evidence suggests that the O_2 cost of walking increases as a function of worsening mobility disability.

Outcomes

The O_2 cost of walking presumably influences fatigue in persons with MS; that is, those who expend more physiological energy during walking probably experience more severe and frequent fatigue. Indeed, fatigue is one of the most commonly reported symptoms of MS, and the O_2 cost of walking may influence the severity of fatigue experienced by a person with MS. We identified two studies examining the relationship between O_2 cost of walking and fatigue. One study examined the association between O_2 cost of treadmill walking and fatigue in 44 persons with mild MS [15]. The results indicated that O_2 cost of walking was positively associated with fatigue ($\rho = .31$), as indicated by scores on the Fatigue Severity Scale (FSS). One final study reported an association between FSS scores and the O_2 cost of walking ($r = 0.22$) in 82 persons with MS [14]. Collectively, the evidence suggests that fatigue severity may be influenced by the O_2 cost of walking and highlight the importance of designing interventions that reduce the O_2 cost of walking to lessen fatigue severity.

Persons with MS who demonstrate higher O_2 cost of walking may be less physically active based on output from accelerometers; accelerometry has been utilized as an appropriate measure of free-living ambulation in persons with MS [16]. One study examined the association between the output from accelerometers and the O_2 cost of walking in a sample of 256 persons with a broad range of MS [16]. There was a significant negative correlation reported between movement counts from the accelerometers and the O_2 cost of walking (ρ = -0.46), suggesting that persons who demonstrate a higher O_2 cost of walking were less physically active under free-living conditions. Another study examined daily activity as a correlate of the O_2 cost of walking in a sample of 44 persons with mild MS [15]. The results indicated that persons who are in the early stages of MS and demonstrate elevated O_2 cost of walking engage in less daily activity based on free-living accelerometry (r = 0.35). This pattern suggests that those who require more energy for walking may have lower levels of physical activity.

Predictors

Persons with MS may demonstrate altered gait patterns in the early stages of the disease, and researchers have suggested a possible relationship among the O_2 cost of walking, spatiotemporal gait parameters, and spasticity in MS. For example, one study examined spatiotemporal gait parameters as variables that explain the association between disability status and O_2 cost of walking in 82 persons with MS [14]. Cadence was identified as the intermediate or mediating variable in the relationship between disability status and O_2 cost of walking; this suggests that cadence should be the target of rehabilitation for reducing O_2 cost of walking as a function of worsening disability in MS. Other researchers

have reported an association between spasticity (i.e., velocity-dependent increase in muscle resistance in response to a passive stretch) and the O_2 cost of walking ($\rho = 0.34$); those with worse spasticity had a higher O_2 cost of walking [17]. Another study examined the relationship between spasticity of the lower extremities and O_2 cost of treadmill walking in 33 persons with MS [18]. The results indicated a significant association between spasticity and O_2 cost of walking in MS ($r = 0.51$). Such results have informed other research that examined spatiotemporal gait parameters as factors explaining the relationship between spasticity and O_2 cost of walking in MS. One paper focused on ankle plantarflexor spasticity and the O_2 cost of walking and examined spatiotemporal gait parameters as possible factors to explain this association in 44 persons with MS who had moderate disability [10]. The results indicated that persons with higher levels of spasticity in the ankle plantarflexors had slower cadence and shorter step length that resulted in a higher O_2 cost of over-ground walking in moderate MS. Such evidence highlights the importance of interventions that target gait and/or spasticity for reducing the O_2 cost of walking in MS.

Gait variability, another quantitative measure of gait for movement consistency or stability, may be associated with a higher O_2 cost of walking. Variability of both stance time and step length have been identified as significant predictors of the O_2 cost of walking in 86 persons with MS [19]. These findings suggest developing interventions that aim to reduce gait variability to lower the O_2 cost of walking in MS.

There is some research focusing on other putative modifiable variables such as fitness parameters that may be associated with the O_2 cost of walking in persons with MS. Indeed, persons with MS demonstrate compromised physical fitness (i.e., aerobic capacity, upper leg muscular strength, and postural control) compared with controls, and the magnitude of reductions in those outcomes increases as a function of worsening disability status. To that end, one study examined aerobic capacity, knee muscular strength, and postural control as correlates of the O_2 cost of walking in 44 persons with MS who have moderate disability based on Expanded Disability Status Scale scores between 4.0 and 6.0 [20]; that is a benchmark of moderate disability reflecting the 2nd stage of MS [21]. Aerobic capacity was measured using an incremental exercise test performed on an electronically braked, computer-driven cycle ergometer with an open circuit spirometry system, knee muscular strength with a computerized dynamometer, and postural control with a force platform. The results indicated that persons who had lower VO_2peak, peak power output, and muscular strength of the knee had greater O_2 cost of walking; however, aerobic power, namely peak power output, was the strongest independent predictor of the O_2 cost of walking in persons with MS. Such results suggest that future research should consider interventions that focus on increasing aerobic power for reducing the O_2 cost of walking in MS.

Management

To date, limited research exists on approaches for reducing the O_2 cost of walking in persons with MS. One study has examined the feasibility of an aerobic treadmill exercise program and its effect on O_2 cost of walking in 3 persons with mild MS [22]. O_2 cost of

walking was calculated from VO_2 and walking speed from 3 minutes of treadmill walking at 4 different speeds, namely 1 $km \cdot h^{-1}$, 3 $km \cdot h^{-1}$, 4 $km \cdot h^{-1}$, and 5 $km \cdot h^{-1}$. The intervention consisted of aerobic training for a total of 10 sessions over a 4-week period. All three participants demonstrated reductions in O_2 cost of walking at 4 $km \cdot h^{-1}$ (from 0.157 to 0.137; 0.169 to 0.146; 0.149 to 0.128), and two of the three participants at 6 $km \cdot h^{-1}$ (from 0.174 to 0.139; 0.198 to 0.17). The results indicate that O_2 cost of walking is reduced following treadmill training in persons with MS. However, the O_2 cost of walking was not measured from steady-state VO_2, and the small sample of persons recruited for the study had mild MS-related disability. There are few rehabilitation options that have been established for the subgroup of persons with MS who have moderate to severe MS; exercise training, as an example of a rehabilitation approach, is typically studied in persons with mild MS [23, 24]. Another study examined the effect of aquatic therapy on the O_2 cost of walking in a mixed sample of 12 persons with MS and spinal cord injury who have spastic paresis [25]. O_2 cost of walking was measured following two weeks of 45-minute hydro-kinesi therapy sessions (i.e., active and passive movements in water). The findings indicate that persons who are characterized by slower self-selected speeds at baseline demonstrate greater reductions in the O_2 cost of walking from the hydro-kinesi therapy compared to those with faster self-selected speeds.

Functional electrical stimulation (FES), a method of delivering electrical stimuli through surface electrodes, and ankle foot orthoses (AFO) have been used to assist with walking for persons with MS and other populations who have drop foot, and research have reported lower O_2 cost of walking while using these devices. We located cross-sectional studies

that compared the O_2 cost of walking with FES and AFO against that of walking without FES and AFO. One study compared the O_2 cost of walking with and without FES in persons with MS who used FES regularly [26]. The results indicated that persons with MS demonstrate lower values of 0.41 (0.15) $ml \cdot kg^{-1} \cdot m^{-1}$ while using FES compared to values of 0.46 (0.16) $ml \cdot kg^{-1} \cdot m^{-1}$ while not using the FES system. Another study examined the O_2 cost of walking for 5 minutes of different speeds with and without FES [27]. Persons with MS demonstrated a lower O_2 cost of walking with the use of FES compared to walking without FES. However, persons with MS who walked at speeds faster than 0.8 $m \cdot s^{-1}$ demonstrated a significant increase in the O_2 cost of walking when using FES. Another cross-sectional study reported that walking with an AFO may reduce the amount of O_2 cost required for walking compared to walking without an AFO in a mixed sample of 10 persons with MS and those post-stroke, possibly as the result of the spring-like characteristic of the AFO reducing the amount of work required for ankle push-off [28].

FUTURE RESEARCH DIRECTIONS

To date, the O_2 cost of walking has not been thoroughly studied in MS. We believe there are more opportunities for research that can identify the degree of change in O_2 cost of walking in MS and its correlates, consequences, and management!

Regarding the expression of the O_2 cost of walking in MS, one research direction involves examining if the O_2 cost of walking differs across sub-populations with MS. For example, researchers might examine if the O_2 cost of walking differs between clinical courses of MS, as relapsing-remitting MS is more commonly studied than progressive

MS, yet progressive courses of the disease often express with more severe mobility disability. Researchers might consider examining the O_2 cost of movement in persons with MS who use wheelchairs for daily mobility; this would require examining the O_2 cost of arm movement for wheelchair propulsion or transport. Other directions include examining the O_2 cost of walking based on demographic characteristics (i.e., age, sex, ethnicity, disease duration), and this is particularly important for age as the population of persons with MS is greying and older age has a number of co-occurring conditions that could influence the energetic cost of walking (e.g., aerobic deconditioning, sarcopenia, and altered gait and balance). Such analyses will help identify the sub-populations of MS who have impaired efficiency with walking and mobility for future, targeted interventions.

The design of targeted interventions requires an understanding of the modifiable correlates of the O_2 cost of walking. One obvious category of modifiable variables involves physical fitness (i.e., peak power output, VO_2peak, muscular strength, postural control); these are characteristic of persons that can become the direct target of exercise training interventions for management of the O_2 cost of walking. Of particular note, future studies might examine ankle plantarflexor strength as a correlate of O_2 cost of walking considering that reduced push-off might influence the worsening of walking impairments in MS [29]. Another related pair of modifiable factors include physical activity and sedentary behavior as overlapping or independent risk factors for an elevated O_2 cost of walking. Other modifiable correlates might include spasticity and gait as well as adiposity and body weight status. There might even be a basis for examining variables from magnetic resonance imaging of the brain and its tracts as correlates of the O_2 cost of walking; this

could inform the study of neurorehabilitation for managing the energetic cost of walking in MS. Clearly, identifying modifiable correlates will inform the development of targeted interventions for possibly reducing the O_2 cost of walking and its consequences in MS.

There are countless opportunities for future research that examines the consequences of the elevated O_2 cost of walking. For example, there should be a strong focus on fatigue as a consequence of O_2 cost of walking in MS, as well as consideration of depression and pain as possible correlates, and potential consequences, of the O_2 cost of walking. Sleep quality and sleep disorders may further be associated directly or indirectly with the O_2 cost of walking in MS. The O_2 cost of walking may further influence employment, participation in the community, and activities of daily living. Of further note, these consequences may negatively influence overall quality of life (QOL) and independence of persons with MS, and those outcomes should be examined as consequences of the O_2 cost of walking.

To date, there is limited research that has examined the effects of exercise programs on O_2 cost of walking in MS, but studies have reported reductions in O_2 cost of walking following exercise programs in persons post-stroke. With the use of FES, persons post-stroke demonstrated lower O_2 cost of walking following a fast treadmill training program through faster and more symmetric walking [30]. Another study compared the effects of a high-intensity treadmill training (HITT) and low-intensity treadmill training (LITT) on O_2 cost of walking in persons post-stroke [31]. Both groups completed sessions 3 times per week for 3 months, and individuals who participated in HITT demonstrated greater

reductions in O_2 cost of walking when compared to those who completed the LITT. As peak power output has been identified as a predictor of O_2 cost of walking in moderate MS [20], we see potential for research conducting interventions that focus on increasing peak power output to reduce the O_2 cost of walking, considering the limited number of interventions in this area and the importance of the consequences of elevated O_2 cost of walking.

Future research might consider two refinements over previous research regarding the mode of exercise interventions for reducing the O_2 cost of walking. The available research that aims to reduce the O_2 cost of walking incorporated treadmill walking as the mode of exercise; however, treadmill walking may not be the most appropriate for persons with moderate mobility disability, or even accessible for those with severe mobility disability. An alternative mode for aerobic training for persons with MS who have moderate to severe mobility disability is a total body recumbent stepper that utilizes both the upper and lower body with coupled arm levers and foot pedals. The total body recumbent stepper has been established as a feasible and valid mode in populations such as post-stroke [32, 33]. Of important note, future research should consider the recruitment of persons who have moderate MS, as this subgroup has a level of disability wherein disease-modifying medications have limited influences on the manifestations of MS [34]. We further note that interventional research should recruit persons with an elevated O_2 cost of walking, as other research in MS does not always pre-screen and recruit persons with a focal problem for randomized controlled trials [24]. Another limitation of previous research is the short duration of the intervention period in MS (e.g., 4 weeks). Exercise in-

terventions of longer periods may yield larger improvements in the O_2 cost of walking and, in turn, clinically meaningful changes in outcomes necessary for improving participation and QOL.

CONCLUSION

Overall, the O_2 cost of walking is higher in persons with MS than healthy persons without MS, even in the early stages of the disease, and it increases as a function of worsening disability status, lower aerobic fitness, gait dysfunction, and spasticity. The higher O_2 cost of walking may result in higher levels of fatigue and reduce participation in free-living daily activities. To date, very few research studies have examined rehabilitation approaches, such as exercise training or other targeted interventions, that may reduce the O_2 cost of walking in MS. To that end, research on therapeutic approaches for reducing the O_2 cost of walking and managing its consequences may advance the management of mobility disability and, ultimately, improve the QOL and independence of persons living with MS.

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Conflict of Interest Statement

None.

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ENERGETIC COST OF WALKING AND ITS PHYSIOLOGICAL CORRELATES IN PERSONS WITH MULTIPLE SCLEROSIS WHO HAVE MODERATE MOBILITY DISABILITY

by

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INTRODUCTION

Walking impairment is one of the most prevalent and life-altering consequences of multiple sclerosis (MS),[1, 2] and the onset may occur in the early stages of the disease,[3] but becomes more prevalent and burdensome with disability progression. For example, persons with MS demonstrate worse walking performance as indicated by 6-minute walk (6MW) distance than healthy controls,[4] and the degree of impairment in 6MW performance worsens as a function of increasing disability status.[5] The impact of reduced walking performance becomes particularly concerning when it co-occurs with an increase in the energetic cost of walking (C_w). C_w represents a physiological marker of walking impairment that reflects the contribution of pathologic gait abnormalities and other manifestations caused by neurological disability.[6] C_w is defined as the amount of oxygen consumed per kilogram of body weight per unit distance traveled ($ml \cdot kg^{-1} \cdot m^{-1}$).[6] Conceptually, C_w reflects the energy required for over-ground and treadmill walking and can increase as a function of shorter distance traveled while expending the same amount of energy, or as a function of increased energy expenditure for walking the same distance.

There is evidence that C_w is higher in persons with MS than controls and is linearly associated with disability status and perhaps other disease-related consequences in persons with MS. One study reported that C_w during treadmill walking was higher in persons with MS than controls.[5] The same study reported that disability status has a positive, linear association with C_w during 6-minute bouts of treadmill and over-ground walking in

persons with MS.[5] C_w during treadmill walking at 54 $m \cdot min^{-1}$ further has been associated with spatiotemporal parameters of gait (i.e., shorter stride length and longer double limb support) measured over-ground at comfortable walking speed in persons with MS;[7] however, it should be noted that treadmill walking at a fixed speed and over-ground walking at comfortable speed may involve substantially different mechanics. Another study overcame the limitation of the aforementioned study by measuring both C_w and gait parameters over-ground and reported that C_w was moderately-to-strongly associated with disability status and spatiotemporal gait parameters in persons with moderate MS-related mobility disability, and cadence, in particular, explained the association between C_w and disability.[8] Collectively, the research demonstrates that C_w is elevated in MS, particularly among those who have mobility disability, and C_w is associated with cadence and other indices of gait (i.e., pathological gait abnormality).

To date, there is minimal research focusing on putative modifiable variables that are associated with elevated C_w in persons with MS who have reached a benchmark of moderate mobility disability characteristic of the 2nd stage of MS based on Expanded Disability Status Scale (EDSS) scores (e.g., EDSS between 4-6).[9] This is important for identifying approaches for reducing C_w and its consequences in MS; C_w has been associated with higher fatigue and interference with daily activities in MS.[7] There are a number of reasons why researchers might focus on metrics of physical fitness (i.e., aerobic capacity, upper leg muscular strength, and postural control) as correlates of C_w in persons with MS who have mobility disability. There are consistent data indicating that physical fitness is compromised in persons with MS compared with controls,[10] and the magnitude of reductions in aerobic capacity, upper leg muscular strength, and postural control increase

as a function of disability status.[11, 12] We further note that physiological conditioning outcomes (i.e., physical fitness) have been associated with 6MW performance in MS,[10] and walking performance is one component of C_w.[5] Physical fitness outcomes have been associated with C_w in other populations including stroke,[13] healthy older adults[14] and adults from the general population.[15] Nevertheless, there have been no direct examinations of physical fitness outcomes as correlates of C_w in persons with MS who have moderate mobility disability.

The current study examined objective measures of aerobic capacity, muscular strength of the knee flexors and extensors, and static postural control as correlates and predictors of C_w in adults with MS who have moderate mobility disability using bivariate correlation and linear regression analyses. We expected that lower levels of aerobic capacity, upper leg muscular strength, and postural control would be associated with a higher C_w. We further expected that aerobic capacity, upper leg muscular strength, and postural control would be independent predictors of C_w, but the exact nature of the associations was not specified a priori, but rather determined through the regression analysis. Such evidence would provide preliminary guidance for the design of an exercise training intervention for targeting C_w in moderate MS disability, as this group has a level of disability wherein disease-modifying medications have limited influence on the manifestations, such as walking impairments and C_w.[9] Few rehabilitation options have been established in this group; exercise, for example, is often studied in persons with mild MS.[16] To that end, identifying domains of physical fitness that might be associated with C_w in persons with moderate MS disability would provide critical information for the development of targeted exercise training interventions (i.e., improving physiological conditioning) for

possibly reducing C_w, and this may result secondary benefits including managing fatigue and maintaining quality of life and independence.

METHODS

Participants

Participants were recruited through newspaper, television, and radio advertisements, as well as e-mail announcements and letters distributed amongst persons in our research database and through the National MS Society. The inclusion criteria were: (a) medical diagnosis of MS confirmed in writing by the participant's neurologist; (b) EDSS score of 4.0 through 6.0 based on clinical evaluation (i.e., a benchmark of moderate mobility disability reflecting the 2nd stage of MS);[9] (c) no relapse over the past 30 days; (d) no symptoms of underlying cardiovascular disease based on the one or fewer affirmatives on the Physical Activity Readiness Questionnaire (PAR-Q); and (e) physician approval for undertaking exercise testing. We included persons irrespective of disease-modifying medications. There were 44 participants who satisfied the inclusion criteria and were subsequently enrolled in the study.

Experimental Protocol

The study and its procedures were approved by a University Institutional Review Board. All participants provided written informed consent and were asked to refrain from physical activity and food-intake 1-3 hours prior to data collection. Data on symptomatic and disease-modifying medications were not recorded. The outcomes were administered on two, non-consecutive days in our laboratory. The order of assessments within and

across days was intentionally designed to reduce fatigue. On day 1, participants initially reported demographic and clinical characteristics. We then measured height and weight using a standard scale stadiometer. This was followed by the 6MW and measurement of C_w using the portable calorimetry system. Participants then underwent isometric dynamometry for measurement of muscular strength of the knee joint. On day 2, participants initially underwent measurement of static postural control, followed by the incremental exercise test for measurement of aerobic capacity. Participants received $50 remuneration for completing the outcomes.

Outcome Measures

C_w. C_w was measured during the 6MW using a portable, indirect calorimetry system (K4b^2 Cosmed, Italy).[a,17] We initially calibrated the spirometer and gas analyzers for the calorimetry system, as per manufacturer's recommendations. We measured oxygen consumption (i.e., VO_2 in $ml \cdot kg^{-1} \cdot min^{-1}$) for an estimate of resting energy expenditure, expressed as the average of two, 30-second values over the last minute of an initial five-minute period of seated rest (i.e., resting-state VO_2). Participants then performed the 6MW along a 75-foot path in a straight, hallway corridor with the instructions of walking as far and as fast as possible for six minutes[4] while wearing the portable calorimetry system for VO_2 measurement over the duration of the 6MW.[4] The use of walking aids among those with EDSS scores of 6.0 was permitted. We measured 6MW distance (m) using a calibrated measuring wheel (Stanley MW50, New Briton, CT).[b] We measured net steady-state VO_2 as the difference between average VO_2 during the last three minutes of the 6MW (i.e., steady-state VO_2) and average resting-state VO_2 values;[5] this controlled

for influences of factors such as physical activity and food intake on energy expenditure. C_w was then expressed as $ml \cdot kg^{-1} \cdot m^{-1}$ by dividing net steady-state VO_2 in $ml \cdot kg^{-1} \cdot min^{-1}$ by actual 6MW speed in $m \cdot min^{-1}$ (C_w = (Steady-state VO_2 – resting VO_2) / speed); we operationalized steady-state VO_2 as the last three minutes of the 6MW based on previous research on oxygen kinetics during 6MW in MS.[6]

Aerobic capacity. Aerobic capacity was measured using an incremental exercise test performed on an electronically braked, computer-driven cycle ergometer (Lode BV, Groningen, The Netherlands)[e] with an open-circuit spirometry system (TrueOne, Parvo Medics, Sandy, UT)[d] for analyzing expired gases. Participants performed a five-minute warm-up at 0 watts (W) and then immediately began the incremental exercise test (i.e., there was no break between warm-up and the test). The initial work rate for the exercise test was 0 W, and the work rate continuously increased at a rate of 15 $W \cdot min^{-1}$ until the participant reached volitional fatigue; this protocol has been validated in persons with MS.[18] We expressed aerobic capacity as peak oxygen consumption (VO_{2peak} in $ml \cdot kg^{-1} \cdot min^{-1}$) and peak power output (W) from the incremental exercise test. VO_{2peak} was recorded based on the highest 20-second VO_2 value when two of the following criteria were met: (1) respiratory exchange ratio ≥1.10; (2) peak heart rate within 10 $beats \cdot min^{-1}$ of age-predicted maximum (i.e., ~1 standard deviation [SD]); or (3) peak rating of perceived exertion ≥ 17. Peak power output was recorded as the highest work rate attained during the exercise test.

Upper leg muscular strength. Bilateral isometric muscular strength of the knee joint was measured using a Biodex System 3 dynamometer (Shirley, NY).[e,19] Participants were positioned and secured to the dynamometer with chest, waist, and thigh straps ac-

cording to the manufacturer's recommendation with the knee flexed at 90° as an anatomical reference, and isometric torque (Nm) was assessed at knee joint angles of 45°, 60°, and 75°. Peak torque was obtained per knee joint angle by having the participant perform a set of three, five-second maximal contractions with the knee extensors immediately followed by another set of three, five-second maximal contractions of the knee flexors. There were no rest periods between contractions within a set, and one-minute rest periods were provided between sets. Participants were given standardized verbal encouragement per repetition. We recorded the highest torque values from each of the three sets of knee extension and knee flexion as measures of upper leg muscular strength.[20]

Postural control. Postural control was measured based on static posturography using a force platform (Bertec Corporation, Columbus, OH).[f] Participants stood without shoes, while wearing an ankle-foot orthosis when applicable, on the force platform and maintain a quiet upright stance with eyes open. We recorded two, 30-second trials, and breaks were given between trials. Postural control was quantified based on motion of the center of pressure (COP); primary outcomes were 95% ellipse of COP sway area (mm^2), mediolateral sway velocity ($mm \cdot s^{-1}$), and anteroposterior sway velocity ($mm \cdot s^{-1}$) averaged across the trials.[21, 22]

Disability status. Participants completed the Patient Determined Disease Steps (PDDS) as an adjuvant for confirming the clinician-based EDSS inclusion criterion.[23] PDDS scores range between 0 (normal) and 8 (bedridden), and the scores have been validated as a measure of disability status in persons with MS.[24]

Statistical Analysis

Data analyses were performed using Statistical Package for the Social Science 24.0.[g] We provided descriptive statistics of the measures as mean (standard deviation, *SD*) unless stated otherwise. The associations between C_w and physical fitness outcomes were examined using Pearson product-moment correlation coefficients (*r*). Values for correlation coefficients were interpreted as small, moderate, and large based on 0.1, 0.3, and 0.5, respectively.[25] We then performed linear regression analysis wherein we regressed C_w on physical fitness outcomes that were significantly associated with C_w in the bivariate correlation analysis with direct entry of variables.

RESULTS

Sample Characteristics

The demographic characteristics of the sample are presented in Table 1. The sample had a mean age of 48 (8.64) years and was predominately female (86%). The mean height and weight were 168 (8.85) centimeters and 84 (25.25) kilograms, respectively. The median EDSS was 5.5, and the median PDDS score was 4.0; both indicated that the sample had moderate mobility disability.

Table 1. Demographic and clinical characteristics of the sample of persons with MS (n=44)

Characteristic	Descriptive Statistic
Age (years)	48.43 (8.64)
Sex [n(%)]	F (38; 86%), M (6; 14%)
Height (cm)	167.80 (8.85)
Weight (kg)	84.23 (25.25)
Patient Determined Disease Steps (0-8)	4.0 (3.0)

Note: Data for age, height, and weight are presented as mean (SD);
Data for PDDS are presented as median (IQR);
F Females, M Males

Descriptive Characteristics

The mean values for C_w and physical fitness outcomes are presented in Table 2. The mean net C_w value was 0.17 (0.07) $ml \cdot kg^{-1} \cdot m^{-1}$ and was higher than reported for adults from the general population and persons with mild MS disability;[5, 11] this was expected as the current sample had mobility disability based on EDSS and PDDS scores. Of note, the distance traveled during the 6MW was 343 ± 159 meters. VO_{2peak} and peak power output values for the present sample were 16.23 (5.86) $ml \cdot kg^{-1} \cdot min^{-1}$ and 86.07 (40.62) W, respectively, and this is significantly lower than that of adults from the general population.[10, 11] Muscular strength of knee extension at 45°, 60°, and 75° were 99.70 (32.89), 115.14 (36.44), and 117.56 (37.47) Nm, respectively, and muscular strength of knee flexion at 45°, 60°, and 75° were 43.47 (17.35), 42.02 (15.69), and 39.30 (14.18) Nm, respectively. Overall, the current sample demonstrated reduced upper leg muscular strength compared with those reported in healthy controls.[26] We further note that the present sample had 95% COP sway area of 1271.60 (1195.71) mm^2, mediolateral sway velocity of 7.27 (3.90) $mm \cdot s^{-1}$, and anteroposterior sway velocity of 15.27 (11.32) $mm \cdot s^{-1}$; these are considerably higher than reported for the general population.[19, 21]

Table 2. Descriptive statistics of physiological measurements of the sample of persons with MS (n=44)

Measurement	Mean (SD)
C_w ($ml \cdot kg^{-1} \cdot m^{-1}$)	0.17 (0.07)
Peak power output (W)	86.07 (40.62)
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	16.23 (5.86)
45° extension (Nm)	99.70 (32.89)
60° extension (Nm)	115.14 (36.44)
75° extension (Nm)	117.56 (37.47)
45° flexion (Nm)	43.47 (17.35)
60° flexion (Nm)	42.02 (15.69)
75° flexion (Nm)	39.30 (14.18)
95% COP sway area (mm^2)	1271.60 (1195.71)
Mediolateral sway velocity ($mm \cdot s^{-1}$)	7.27 (3.90)
Anteroposterior sway velocity ($mm \cdot s^{-1}$)	15.27 (11.32)

Note: SD Standard Deviation

Bivariate Correlation Analysis

The bivariate associations between C_w and physical fitness outcomes are provided in Table 3. C_w was inversely correlated with VO_{2peak} (r=–.31, p<0.05), peak power output (r=–.55, p<0.01), and peak torque of 75° knee flexion (r=–.34, p<0.05), whereas C_w was positively correlated with 95% COP sway area (r=.32, p<0.05) and mediolateral sway velocity (r=.41, p<0.05). The correlations involving VO_{2peak}, 75° knee flexion, 95% COP sway area, mediolateral sway velocity, and C_w were moderate in magnitude, whereas the correlation involving peak power output and C_w was large in magnitude.

Table 3. Summary of correlations among C_w and physiological measurements in the sample of persons with MS (n=44)

	1	2	3	4	5	6	7	8	9	10	11	12
1. C_w ($ml \cdot kg^{-1} \cdot m^{-1}$)	--	--	--	--	--	--	--	--	--	--	--	--
2. VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	-0.31*	--	--	--	--	--	--	--	--	--	--	--
3. Peak power output (W)	-0.55*	0.75*	--	--	--	--	--	--	--	--	--	--
4. 45° extension (Nm)	-0.19	0.24	0.40*	--	--	--	--	--	--	--	--	--
5. 60° extension (Nm)	0.16	0.22	0.39*	0.94*	--	--	--	--	--	--	--	--
6. 75° extension (Nm)	-0.13	0.25	0.47*	0.85*	0.94*	--	--	--	--	--	--	--
7. 45° flexion (Nm)	-0.21	0.33*	0.42*	0.81*	0.84*	0.81*	--	--	--	--	--	--
8. 60° flexion (Nm)	-0.28	0.37	0.50	0.77*	0.83*	0.83*	0.96*	--	--	--	--	--
9. 75° flexion (Nm)	-0.34*	0.45*	0.56*	0.73*	0.79*	0.81*	0.88*	0.95*	--	--	--	--
10. 95% COP sway area (mm^2)	0.32*	0.05	-0.12	-0.21	-0.26	-0.29	-0.20	-0.26	-0.25	--	--	--
11. ML sway velocity ($mm \cdot s^{-1}$)	0.41*	0.01	-0.19	-0.24	-0.30	-0.34*	-0.31*	-0.39*	-0.35*	0.91*	--	--
12. AP sway velocity ($mm \cdot s^{-1}$)	0.17	0.28	-0.03	-0.03	-0.08	-0.16	-0.03	-0.15	-0.11	0.74*	0.78*	--

Note: *$p < 0.05$; COP Center of Pressure, ML Mediolateral, AP Anteroposterior

Linear Regression Analysis

The results of the regression analysis are provided in Table 4. We regressed C_w on peak power output, peak torque of 75° knee flexion, and mediolateral sway velocity; we selected this subset for avoiding multicollinearity (i.e., the correlation between peak power output of VO_{2peak} was r = .75 in the bivariate analysis, for example, and would present considerable threat toward multicollinearity) and because those were the strongest correlates of C_w per category of physical fitness variables (i.e., aerobic capacity, upper leg muscular strength, postural control). The model was statistically significant ($F_{3,36}$=8.09, p<0.01) and explained 40.3% of variance in C_w (R^2=.403). Peak power output was the primary correlate of C_w (β=–.526, p<0.01), and mediolateral sway velocity further was identified as a significant correlate of C_w (β=.339, p<0.05). Peak torque of 75° flexion was not significantly associated with C_w in the regression analysis that included peak power output or mediolateral sway velocity.

Table 4. Summary of linear regression analysis for variables predicting C_w in the sample of persons with MS (n=44)

	C_w		
	B	SE *B*	β
Peak power output (W)	-0.001	0.000	-0.526*
75° flexion (Nm)	0.000	0.001	0.074
ML sway velocity ($mm \cdot s^{-1}$)	0.007	0.003	0.339*

Note: *p<0.05; *B* Unstandardized Beta, SE *B* Standard Error of Beta, β Standardized Beta

DISCUSSION

This study examined physical fitness outcomes as correlates and predictors of C_w in adults with moderate mobility disability based on EDSS scores between 4.0 and 6.0.

The present sample of persons with MS who had moderate disability demonstrated higher values of C_w,[5] lower aerobic capacity,[11] reduced muscular strength,[26] and worse postural control[21] compared to those without MS, consistent with previous research. The bivariate correlation analysis indicated that persons who had lower VO_{2peak}, peak power output, and muscular strength of the knee flexors had a greater C_w. The bivariate correlation analysis further indicated that those with greater postural instability (i.e., greater COP sway area and mediolateral sway velocity) had higher C_w. The linear regression analysis indicated that only peak power output and mediolateral sway velocity independently explained significant variance in C_w in this sample of adults with MS who had mobility disability. Such results suggest that peak power output and mediolateral sway velocity may be unique correlates of C_w that could be targeted in future rehabilitation interventions.

Peak power output reflects a person's physiological function reserve (i.e., performance capacity) and may have direct relevance for understanding the penalty of walking impairment on the energetic demands of walking, as it is predictive of functional limitations and required for undertaking activities of daily living.[27] Indeed, the influence of reduced physiological function reserve on higher C_w may be a function of both reduced walking distance and increased energy expenditure.[5] The association between mediolateral sway velocity and C_w suggests that inefficiency in controlling the trajectory of the body's center of mass may have relevance for the energetic demands of walking. This may translate into a greater expenditure of energy during walking based on inefficiency for forward motion during ambulation resulting in excess energy expenditure per unit walked, and possibly be a by-product of shorter stride length and longer double limb support resulting in reduced walking speed, as demonstrated in mild MS;[7] however, it should

be noted that this association between C_w and gait parameters may have been influenced by demand characteristics (i.e., measurement of C_w during fixed treadmill walking and measurement of gait during comfortable walking speed over-ground). Nevertheless, this association has been replicated in a separate sample of persons with MS wherein both variables were measured based on over-ground walking.[8] Persons with moderate MS demonstrate altered gait parameters (i.e., reduced cadence, shorter stride length, prolonged double limb support).[28] By extension, perhaps there is an association between C_w and gait parameters in persons with moderate MS. Collectively, reduced peak power output and increased mediolateral sway velocity reflect performance decrements in MS that have direct relevance for inefficiency with expending energy during walking, and represent targets not only for improving walking performance but further walking efficiency.

The regression analysis, of note, indicated there was no association between C_w and peak torque of 75° knee flexion, when accounting for peak power and mediolateral sway velocity. This suggests that greater strength of the knee flexors does not necessarily correlate with lower C_w in persons with MS who have moderate mobility disability. There further were no significant bivariate correlations between C_w and other strength variables in this sample. To our knowledge, limited research has addressed the relationship between knee flexion strength across different joint angles and C_w in MS or other populations. We do note that knee flexion strength is consistently associated with walking performance in many chronic diseases including MS,[29, 30] and this may be associated with efficiency of muscle activation and/or the length-tension relationship[31] for the hamstring muscles. Although muscular strength of the knee flexors was not a predictor of C_w in the current study, some researchers have reported that knee flexor strength is a predic-

tor of walking capacity and determinant of walking speed in persons with MS and those with moderate MS-related disability.[20, 32] This implies that, whereas upper leg muscular strength may be a determinant of walking performance in persons with MS, it might not directly influence the energetic cost of movement itself (i.e., it does not translate into inefficiency).

There is limited evidence on actual exercise training approaches for reducing C_w in persons with MS who have moderate mobility disability. We believe that such interventions might target aerobic power and postural control, more specifically mediolateral sway velocity, given that these two domains of physiological conditioning are reduced in MS as a function of mobility disability,[11, 12] and further were independent predictors of C_w in the present study. Our results suggest that improvements in aerobic power and mediolateral sway brought about by targeted interventions may yield reductions in C_w in people with MS who have mobility disability. An approach for maximizing adaptations of peak power output involves aerobic training,[33, 34]; such adaptations further might be optimized through high-intensity interval training. This form of training involves a high-intensity training stimulus brought about by periods of near maximal work rates, and one recent study reported that high-intensity interval training was associated with substantial adaptations in measures of aerobic capacity in persons with MS.[35] By comparison, there is no evidence of an optimal modality and intensity for a postural control exercise program for reducing C_w. Accordingly, researchers might consider examining the independent and additive effects and mechanisms of aerobic exercise training and postural control training for reducing C_w and its secondary outcomes in persons with MS who have mod-

erate mobility disability, considering that these two domains of physiological conditioning explained approximately 40% of variance in C_w in the current study.

Study Limitations

There are important limitations that should be considered when interpreting and generalizing the results of this study. The cross-sectional study design is a limitation and cannot identify causality between C_w and physical fitness outcomes. However, such a cross-sectional examination can represent a precursor for the design of longitudinal interventions that target selective domains of physiological conditioning for reducing C_w. This study did not examine the underlying mechanisms that may reduce the C_w in MS, but rather focused on modifiable determinants. The present study involved a relatively small sample size and involved the *a priori* recruitment of persons with moderate MS-related mobility disability. This limits the generalizability of the results among adults with mild or severe MS-related disability. We note that substantial variability in our measures was present in our sample; this is consistent of a population with moderate MS wherein heterogeneity in ambulatory outcomes would be expected. This variability further is important when examining correlations among variables, as truncated dispersion of scores biases or attenuates correlations toward zero and erroneous failure for rejecting the null hypothesis. Regarding our protocol, we opted for the use of a cycle ergometer instead of a treadmill for the measurement of aerobic capacity. This was necessary for controlling potential confounding factors (e.g., symptomatic fatigue) and maximizing safety for those with MS-related mobility disability (e.g., drop-foot). Another limitation of our protocol is that we did not assess the strength of other muscle groups aside from the knee flexors and ex-

tensors. There is an established body of research examining knee joint muscular strength as correlates of walking in many chronic diseases,[36, 37] including MS,[32] and this large muscle group could explain variation in C_w in moderate MS disability. Poor knee strength can reduce the swing phase of the gait cycle and has been reported to be a main predictor of worse walking capacity in persons with moderate MS.[20] Nevertheless, future researchers might focus on the ankle plantarflexors muscular strength as a correlate of C_w considering that reduced push-off (i.e., poor ankle plantarflexor functioning) might contribute to worsened MS-related walking impairment.[38] Another limitation includes the measurement of COP area while standing still (i.e., static posturography). Given that individuals with MS have compromised static postural control, it may be expected that under a situation when the body is in motion (i.e., walking) dynamic postural control may be compromised as well if not even more so. Future research examining correlates of C_w in MS might consider examining the differences between modalities of aerobic capacity measurement (e.g., treadmill) and add multidimensional measures of postural control (e.g.., dynamic posturography during the 6MW) in addition to static posturography.

CONCLUSION

The present study provides the first data on the associations among C_w and physical fitness outcomes in persons with MS who have reached a benchmark of moderate mobility disability, and our results highlight that peak power output and mediolateral sway velocity are important correlates of C_w in this population. Future research efforts might consider examining the influence of high-intensity interval training and/or postural control training as rehabilitative approaches for increasing aerobic capacity, reducing

postural instability, and ultimately reducing C_w in persons with MS who have moderate mobility disability. Such interventions designed to reduce C_w might further result in secondary benefits that are important for maintaining quality of life and independence in this segment of persons with MS.

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ENERGETIC COST OF WALKING AND SPASTICITY IN PERSONS WITH MULTIPLE SCLEROSIS WITH MODERATE MOBILITY DISABILITY

by

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INTRODUCTION

Multiple sclerosis (MS) is a chronic neurological disease characterized by immune-mediated demyelination and neurodegenerative processes (i.e., axonal transection and neuronal loss) in the central nervous system (CNS) (Trapp & Nave, 2008). The disease process manifests as white and gray matter damage in the CNS and results in mobility disability (Motl, 2010). Walking impairment is one of the most ubiquitous and life-altering consequences of MS and worsens as a function of increasing mobility disability (Larocca, 2011; Motl et al., 2017). Walking impairment may become particularly problematic when it co-occurs with an increase in energetic cost of walking (C_w). C_w (i.e., the amount of oxygen consumed per kilogram of body weight per unit distance walked) is a physiological marker of walking impairment that reflects the contributions of pathological gait abnormalities and other manifestations caused by disability (Waters & Mulroy, 1999). There is evidence that persons with MS have higher C_w than persons without MS (Chung, Angelo, van Emmerik, & Kent, 2016; Motl et al., 2011), and that among persons with MS, those with worse walking impairment demonstrated higher C_w measured during both treadmill and over-ground walking (Motl et al., 2011). One subgroup of persons with MS that has been identified to have particularly elevated C_w involves those who have reached the onset of moderate mobility disability (i.e., Expanded Disability Status Scale [EDSS] scores ≥ 4.0). Elevated C_w associated with moderate MS-related mobility disability might lead to reduced participation in daily activities and possibly increased perceptions of fatigue (Motl, Sandroff, Suh, & Sosnoff, 2012). Such observations support

the importance of research that identifies factors associated with C_w for informing the design of future rehabilitation interventions that target a reduction in walking impairment and its consequences among persons with MS.

Spasticity (i.e., velocity-dependent increase in muscle resistance in response to a passive stretch) is a common symptom of MS and may influence C_w (Johnson, 2002). Spasticity is linearly associated with mobility disability and is most prevalent in the ankle plantarflexors (Hoang, Gandevia, & Herbert, 2014; Rizzo, Hadjimichael, Preiningerova, & Vollmer, 2004). For example, persons with MS who have spasticity of ankle plantarflexors have demonstrated reduced walking performance based on the 6-Minute Walk (6MW), Timed 25-Foot Walk (T25FW), and Timed Up and Go (TUG) compared with those who do not have spasticity (Olgiati, Burgunder, & Mumenthaler, 1988; Sosnoff, Sandroff, & Motl, 2012). Spasticity of the ankle plantarflexors further has been associated with higher C_w while walking on a treadmill in a small sample of 33 persons with MS who had mild disability (Olgiati et al., 1988). Of note, C_w measured on a treadmill may not be comparable to that of over-ground walking in persons with MS (Motl et al., 2011). There is minimal research examining spatiotemporal gait parameters (i.e., cadence and step length) as possible factors accounting for the relationship between plantarflexor spasticity and C_w in persons with MS who have moderate mobility disability.

The association between spasticity of the ankle plantarflexors and C_w may be explained by alterations in spatiotemporal gait parameters (Haselkorn & Loomis, 2005; Thompson, Jarrett, Lockley, Marsden, & Stevenson, 2005). One study indicated that persons with MS who have spasticity demonstrate reduced walking velocity, cadence, and step length compared with those who do not have spasticity (Pau, Coghe, Corona,

Marrosu, & Cocco, 2015). There further is evidence of an inverse relationship between spatiotemporal gait parameters and C_w (Motl et al., 2012). Cadence, in particular, has explained the association between disability status and C_w (Sandroff, Klaren, Pilutti, & Motl, 2014). Collectively, such a pattern of results suggests that spasticity may influence C_w and ultimately mobility disability through alterations in gait parameters. However, we are unaware of direct examinations of C_w and its associations with spasticity and spatiotemporal gait parameters in persons with moderate MS mobility disability.

The current study examined the associations among C_w, spasticity of the ankle plantarflexors, and spatiotemporal gait parameters in persons with MS who had moderate mobility disability based on scores between 4.0 and 6.0 from the EDSS (i.e., a benchmark of moderate mobility disability indicative of the 2nd stage of MS), as this group has a level of disability wherein disease-modifying medications have limited influence on manifestations such as walking impairments and C_w (Confavreux, Vukusic, & Adeleine, 2003). We hypothesized that higher levels of spasticity of the ankle plantarflexors would be associated with higher C_w measured during over-ground walking. We further hypothesized that higher levels of spasticity would be associated with worse alterations in spatiotemporal gait parameters, particularly cadence and step length, and that the alterations in spatiotemporal gait parameters would account for the association between spasticity of the ankle plantarflexors and C_w. If our hypotheses are correct, such preliminary evidence would highlight the importance of developing therapeutic, rehabilitation interventions for eventual inclusion in clinical practice for managing spasticity as an approach for reducing C_w and ultimately walking impairment by improving gait. Such interventions may result

in secondary benefits including management of fatigue and improvement in quality of life in persons with moderate MS.

METHODS

Participants

The participants were recruited through direct contact with support groups of a Midwestern chapter of the National Multiple Sclerosis Society that were located with an approximately 90-minute drive of the testing facility. The inclusion criteria involved (a) medical diagnosis of MS; (b) EDSS score between 4.0 and 6.0 confirmed based on the participants' neurologist; (c) relapse-free during the past 30 days before testing; (d) ambulation without an assistive device including cane, crutch or walker; (e) willingness to complete the walking assessments; and (f) low risk for contraindications of physical activity based on no more than a single "yes" response on the Physical Activity Readiness Questionnaire (PAR-Q) (Thomas, Reading, & Shephard, 1992).

The sample had a mean (standard deviation, SD) age of 48 (8.6) years and was predominantly female (86%). The mean height and weight were 168 (8.8) centimeters and 84 (25.2) kilograms, respectively. The median (interquartile range, IQR) PDDS score was 5.5 (2.5) indicating that the sample had moderate mobility disability (Learmonth, Motl, Sandroff, Pula, & Cadavid, 2013).

Outcome Measures

Spasticity. Spasticity of the ankle plantarflexors of both legs were measured by a physical therapist using the modified Ashworth scale (MAS). The MAS provides a meas-

ure of muscle hypertonia on a five-point scale, ranging from 0 (no increase in muscle tone) through 4 (fixed muscle contracture) (Bohannon & Smith, 1987). We averaged the MAS scores for plantarflexors of both legs for the data analysis. This was based on providing a global measure of spasticity of the plantarflexors, and the observation that the MAS score of the most affected leg correlated with the average MAS score (r=.97). The intraclass correlation for MAS scores from the right and left legs was .90 and further supported the formation of an average MAS score.

Energetic cost of walking. C_w was measured during the 6MW using a portable, indirect calorimetry system (K4b2 Cosmed, Italy). The O_2 and CO_2 analyzers and flowmeter of the portable metabolic unit were calibrated, as per manufacturer's recommendations. We measured oxygen consumption for an estimate of resting metabolic function, expressed as the average of two, 30-second values over the last minute of an initial five-minute period of seated rest (i.e., resting-state VO_2). Participants then underwent the 6MW with standardized instructions of walking as far and as fast as possible for six minutes while wearing the portable calorimetry system for VO_2 measurement. Total distance traveled (m) was measured using a calibrated measuring wheel (Stanley MW50, New Briton, CT). We measured net steady-state VO_2 as the difference between average VO_2 during the last three minutes of the 6MW (i.e., steady-state VO_2) and average resting-state VO_2 values. C_w was then expressed as $ml \cdot kg^{-1} \cdot m^{-1}$ by dividing net steady-state VO2 in $ml \cdot kg^{-1} \cdot min^{-1}$ by actual 6MW speed in $m \cdot min^{-1}$ (C_w = (steady-state VO_2 – resting VO_2) / speed); we operationalized steady-state VO_2 as the last three minutes of the 6MW based on previous research regarding the pattern of oxygen kinetics during the 6MW in

MS and our current data wherein steady-state was clearly obtained by 180 seconds of the 6MW.

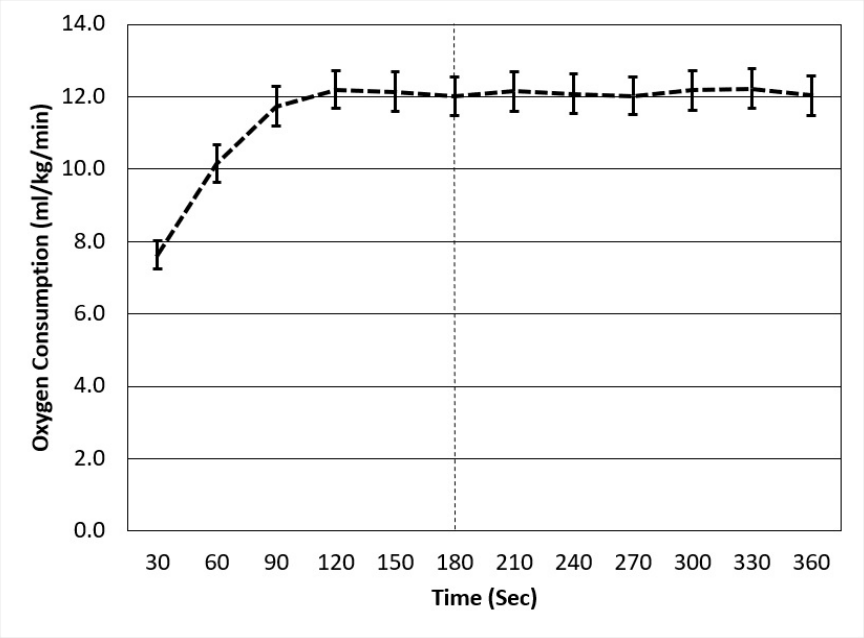

Figure 1. Oxygen consumption over a six-minute walk test in the sample of persons with MS.

Gait parameters. Participants completed 4 trials of walking on a 16-foot GAITRite (CIR systems, Inc, Havertown, Pennsylvania) electronic walkway at a comfortable pace as done in previous research involving persons with MS (Sosnoff, Gappmaier, Frame, & Motl, 2011; Sosnoff et al., 2012). The GAITRite system is a computerized instrumented mat with sensors arranged in a grid-like pattern for identifying footfall contacts. We recorded cadence (steps/min) and step length (cm) per trial based on previous research involving gait and C_w in MS (Sosnoff et al., 2012), and the average of the 4 trials was used in the data analysis.

Disability status. Participants completed the Patient Determined Disease Steps (PDDS) as an adjuvant for confirming the EDSS inclusion criterion (Marrie & Goldman,

2007). PDDS scores range between 0 (normal) and 8 (bedridden), and the scores have been validated as a measure of disability status in persons with MS (Learmonth et al., 2013).

Procedure

The procedure was approved by a University Institutional Review Board, and all participants provided written informed consent. Participants completed a demographic scale, underwent a measurement of spasticity of the ankle plantarflexors using the Modified Ashworth Scale (MAS) by a physical therapist, and performed 4 trials of walking on the GAITRite electronic walkway for measuring spatial and temporal parameters of gait followed by 10 minutes of seated rest. We measured height and weight using a scale stadiometer. Participants were then fitted with the portable metabolic system during the seated rest. Once wearing the system and ensuring normal, resting metabolic function, participants were given standardized instructions for undertaking the 6MW test. All participants were remunerated $50 for completing the session.

Statistical Analysis

All data analyses were performed using Statistical Package for the Social Science 24.0. We provided descriptive statistics of the measures as mean (standard deviation, SD) unless stated otherwise. The associations among C_w, ankle plantarflexor spasticity, and gait parameters were examined using Pearson product-moment correlation coefficients (r). Values for correlation coefficients were interpreted as small, moderate, and large based on 0.1, 0.3, and 0.5, respectively (Cohen, 1988). To identify if gait parameters (i.e.,

cadence and step length) accounted for the association between ankle plantarflexor spasticity and C_w in our sample, we performed a hierarchical linear regression analysis wherein we regressed C_w on ankle plantarflexor spasticity in Step 1, followed by stepwise entry of cadence and step length as predictors in Steps 2 and 3, respectively.

RESULTS

Descriptive Characteristics

The mean values for ankle plantarflexor spasticity, cadence, step length, and C_w are presented in Table 1. The median (IQR) MAS value of the sample was 1.50 (1.88); this corresponds with a MAS anchor of "slight increase in muscle tone, manifest as a catch and release or resistance at the end of range of motion during passive movement" (Bohannon & Smith, 1987). The mean cadence value was 95.25 (20.26) steps per minute, and the mean step length value was 53.80 (14.75) centimeters. Overall, this sample demonstrated reduced cadence and step length compared with other MS samples (Sandroff, Sosnoff, & Motl, 2013); this was expected as the current sample had moderate mobility disability based on EDSS and PDDS scores. Of note, the mean net C_w value was 0.17 (0.07) $ml \cdot kg^{-1} \cdot m^{-1}$; this value is comparable with C_w reported in another sample of persons with a broad range of MS-related mobility disability (Sandroff et al., 2014).

Table 1. Descriptive statistics of spasticity, cadence, step length, and C_w of the sample of persons with MS (n=44)

Measurement	Mean (SD)
MAS	1.59 (1.04)
Cadence (steps/min)	95.25 (20.26)
Step length (cm)	53.80 (14.75)
C_w ($ml \cdot kg^{-1} \cdot m^{-1}$)	0.17 (0.07)

Note: Mean (SD); MAS, Modified Ashworth Scale

Bivariate Correlation Analysis

The bivariate associations among spasticity, cadence, step length, and C_w are provided in Table 2. Spasticity was positively correlated with C_w (r=.52, p<0.05) and inversely correlated with cadence (r=−.45, p<0.05) and step length (r=−.40, p<0.05). Cadence (r=−.59, p<0.05) and step length (r=−.56, p<0.05) were inversely correlated with C_w. Collectively, this indicates that those with greater spasticity demonstrated moderately higher C_w, slower cadence, and shorter step length.

Table 2. Summary of correlations among spasticity, cadence, step length, C_w, in the sample of persons with MS (n=44)

	1	2	3	4
1. MAS	--	--	--	--
2. Cadence (steps/min)	-0.45*	--	--	--
3. Step length (cm)	-0.40*	-0.40*	--	--
4. C_w ($ml \cdot kg^{-1} \cdot m^{-1}$)	0.52*	-0.59*	-0.56*	--

Note: MAS, Modified Ashworth Scale; *p<0.05, two-tailed test

Regression Analysis

The results of the regression analyses are provided in Table 3. The first model indicated that ankle plantarflexor spasticity had a significant association with C_w and explained 27.2% of variance in C_w (R^2 = .272, p < 0.01; $F_{1,43}$ = 15.73, p < 0.01) (Step 1). Cadence entered into the equation in Step 2 (ΔR^2 = 0.162, p < 0.01), and the model explained 43.5% of variance in C_w (R^2 = .435, p < 0.01; $F_{2,42}$= 15.77, p < 0.01). Both cadence and step length entered into the equation in Step 3 (ΔR^2 = .066, p < 0.03), and the model explained 50.1% of variance in C_w (R^2 = .501, p < 0.05; $F_{3,40}$ = 13.40, p < 0.00). The standardized beta-coefficient between C_w and ankle plantarflexor spasticity in Step 1

was attenuated and non-significant when controlling for cadence and step length in the model in Steps 2 and 3.

Table 3. Summary of regression analysis for spasticity, cadence, and step length predicting C_w in the sample of persons with MS (n=44)

	C_w		
	B	SE *B*	β
Step 1			
MAS	0.039	0.010	0.522*
Note: R^2 = .272 for model (p < .01)			
Step 2			
MAS	0.024	0.010	0.320*
Cadence	-0.002	0.000	-0.451*
Note: R^2 = .435 for model (p < .01)			
Step 3			
MAS	0.018	0.010	0.248
Cadence	-0.001	0.001	-0.339*
Step length	-0.002	0.001	-0.302*
Note: R^2 = .501 for model (p < .05)			

Note: MAS, Modified Ashworth Scale; *p<0.05; *B* Unstandardized Beta, SE *B* Standard Error of Beta, β Standardized Beta

DISCUSSION

This study examined the association between ankle plantarflexor spasticity and C_w in persons with MS who had moderate mobility disability, and further examined spatiotemporal gait parameters as possible factors that accounted for the association between spasticity and C_w. The bivariate correlation analysis indicated that persons who had higher levels of spasticity in the ankle plantarflexors demonstrated higher C_w during a 6-minute period of walking, as well as slower cadence, and shorter step length under normal walking conditions. The regression analysis indicated that ankle plantarflexor spas-

ticity explained significant variance in C_w in persons with MS who had moderate mobility disability, and cadence and step length accounted for this association. Such results suggest that worse spasticity is associated with higher C_w possibly through altered spatio-temporal gait parameters and identify spasticity of the ankle plantarflexors as a target for subsequent therapeutic rehabilitation interventions for reducing C_w and improving gait among those with the onset of moderate MS-related mobility disability.

Spasticity of the ankle plantarflexors was significantly associated with C_w measured during over-ground walking in the present sample of persons with moderate MS. To our knowledge, this study is the first to examine spasticity and C_w during over-ground walking in those who have moderate mobility disability based on EDSS scores between 4.0 and 6.0 and then confirmed with PDDS scores. One previous study identified an association between spasticity and C_w on a treadmill in thirty-three persons with mild MS (Olgiati et al., 1988), but did not include a standard, clinical measure of spasticity. We extended that research by including persons with moderate MS who undertook over-ground walking, and our results confirm this association between a clinically-relevant measure of ankle plantarflexor spasticity and C_w. MS-related spasticity that occurs during walking may increase C_w based on varying displacement of center of gravity during walking, resulting in a less efficient walking pattern. As such, the current results suggest that management of ankle plantarflexor spasticity may be a target for possibly reducing C_w in MS.

Spasticity of the ankle plantarflexors was associated with alterations in cadence and step length in the present sample of persons with moderate MS-related mobility disability. This is consistent with results from a previous study in MS that reported that nine-

teen persons with MS who had moderate-to-severe spasticity in the plantarflexors demonstrated reduced cadence and stride length measured by a 3D motion analysis system (Pau et al., 2015). Indeed, the present results extend this relationship by demonstrating associations among spasticity, cadence/stride length, and C_w among persons with moderate MS-related mobility disability. This further supports the observation of altered gait parameters in persons with MS who have EDSS scores between 4.0 and 6.0 (Pilutti et al., 2013). We speculate that persons with MS within this range who demonstrate slower cadence and shorter stride length may do so, in part, because of higher levels of spasticity. As previous studies have reported, the presence and severity of spasticity is significantly associated with disability status (Rizzo et al., 2004), which suggests that alterations in gait parameters may be more distinctive and detrimental as disability worsens. This underscores the importance of designing interventions for the management of spasticity for maintaining or improving gait parameters.

Cadence and step length were associated with C_w in this sample of persons with MS who had moderate mobility disability, and this is consistent with previous research. For example, a previous study reported an association between cadence and C_w measured on a treadmill in forty-four persons with mild MS (Motl et al., 2012). We have extended the results of previous research by demonstrating that cadence and stride length were associated with C_w measured during over-ground walking in persons with MS who have moderate mobility disability. We do note that our protocol involved walking over-ground, as opposed to on a treadmill, as this better reflects free-living walking in persons with MS. Nevertheless, the current pattern of results is consistent with the notion that C_w

reflects the overarching contribution of disability on walking impairments in neurological diseases (Waters & Mulroy, 1999).

The primary novel findings were that ankle plantarflexor spasticity was associated with C_w, and that cadence and step length explained the association between spasticity and C_w. The identification of cadence and step length as intervening variables of the association between spasticity and C_w may be attributed to inefficient walking patterns resultant from spasticity of the plantarflexors, which may, in turn, reduce cadence and step length. This indicates that altered spatiotemporal gait parameters might result in the energetic penalty of walking brought upon by spasticity in those with MS who have moderate mobility disability. The current results support the development of interventions for managing spasticity and, in turn, improving cadence and step length to minimize the C_w in MS, particularly those with moderate mobility disability that is characteristic of the 2nd stage of the disease.

There are limitations that should be considered when interpreting the results of this study. One limitation includes the cross-sectional study design, which does not provide longitudinal data on the management of spasticity and alterations of gait parameters on C_w. Another limitation of the study is that we did not include other variables that may have affected gait in MS aside from spasticity of the ankle plantarflexors as potential covariates; this was based on the hypothesis that gait and spasticity are major contributors of C_w and the lack of exploratory research for identifying the possible variables explaining C_w in MS. We note that future research efforts might consider identifying and controlling for such potential covariates when examining the effects of gait on C_w in persons with MS. However, spasticity is commonly observed in persons with MS and has been

reported to result in negative consequences on mobility and balance (Rizzo et al., 2004; Sosnoff et al., 2011). The study further does not indicate causality among ankle plantarflexor spasticity, spatiotemporal gait parameters, and C_w, but does provide preliminary data that is precursory for designing an intervention that targets the management of spasticity and gait rehabilitation for reducing C_w. One final limitation involves a relatively small sample size that was specifically recruited based on having the onset of moderate MS-related mobility disability, which limits the generalizability among those with mild or severe MS.

The present study reported that spasticity of the plantarflexors was associated with higher C_w and that spatiotemporal gait parameters account for this association in persons with MS who have moderate mobility disability. Both spasticity and gait parameters were associated with C_w, and cadence and step length explained the association between spasticity and C_w. Collectively, these results suggest that worse spasticity of the plantarflexors and slower cadence and shorter step length, in turn, are responsible for elevated C_w among persons with moderate MS. This supports the application of an intervention for managing spasticity to possibly reduce C_w that may interfere with activities of daily living in persons with MS.

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OXYGEN COST OF WALKING IN MULTIPLE SCLEROSIS: ASSOCIATIONS WITH BODY COMPOSITION AND DISEASE-RELATED OUTCOMES

by

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INTRODUCTION

Multiple sclerosis (MS) is a chronic neurological disease characterized by demyelination and transection of axons as well as loss of neurons in the central nervous system with a prevalence of approximately 1 million people in the United States and 2.3 million people worldwide.[1, 2] One hallmark feature of MS is walking impairment,[3] even in the early stages of the disease.[4] Walking impairment often results from changes in gait, including reduced stride length and cadence.[5] Walking impairment might become particularly troublesome in MS when it occurs with poor walking efficiency, as indicated by an increase in the oxygen (O_2) cost of walking (C_w).

C_w is defined as the amount of oxygen consumed per kilogram of body weight per unit distance walked, and reflects the contributions of disability-related gait abnormalities and manifestations and its interaction with external constraints.[6] Collectively, there is evidence that C_w is higher in persons with MS than healthy controls and is linearly associated with disability status and perhaps other disease-related consequences.[7-9] Persons with MS who have higher C_w further have lower levels of daily physical activity and worse fatigue.[8] Other correlates of higher C_w include reduced cadence, shorter step length, worse spasticity, and lower peak aerobic capacity.[8, 10, 11] There is relatively little known about pain, depression, anxiety, and quality of life as correlates of C_w in MS.[12]

Body composition may be another correlate of C_w in persons with MS. To date, there are few studies examining the relationship between body composition and C_w. For example, one study has examined C_w in persons with MS based on body mass index

(BMI) categories of normal weight, overweight, and obese, and reported a trend whereby persons with lower BMI demonstrated elevated C_w.[13] However, the study utilized BMI, calculated from height and weight, as a measure of body composition. BMI has advantages of cost-effectiveness and ease of administering. However, the current categories of BMI significantly underestimate adiposity in persons with MS; this can lead to possible misclassifications of persons with MS in the obese category as non-obese.[14] Dual-energy x-ray absorptiometry (DXA) is considered the gold standard method of measuring body composition outcomes and has the capability to differentiate fat mass, fat-free mass, and bone mineral content of the body.[15] Such a methodology affords the opportunity to provide a stronger understanding of body composition as a correlate of C_w in MS.

The present study examined the relationships among C_w, body composition metrics, and MS-related outcomes, while considering potential covariates such as physical activity, spasticity, and gait based on previous research.[8, 10] This study was the first step in better understanding the relationship among those variables for possibly developing health-promoting lifestyle interventions targeting body composition for improving walking efficiency and quality of life in persons with MS. If this study identifies a body composition outcome as a correlate of C_w, this would underscore the importance of developing interventions that target the optimization of body composition profiles for the management of C_w in MS.

METHODS

Participants

Persons with MS were recruited through word-of-mouth and flyers in the community, support groups, and local neurology clinics. We targeted a sample of 60 participants across a range of BMI categories (20 persons of normal [18.5-24.9 kg/m^2], overweight [25-29.9 kg/m^2], and obese [>30 kg/m^2] status) for generating a wide distribution of body composition metrics. Inclusion criteria were as follows: (1) diagnosis of MS; (2) age of at least 18 years; (3) no relapse or sudden change in MS symptoms within the last 30 days; (4) ability to ambulate either with or without the use of an assistive device; (5) no pregnancy. Participants who did not meet these criteria were excluded from the study. Of 127 persons who contacted the research team, 85 persons were assessed for eligibility. We lost contact with 9 persons after screening, and 12 persons were excluded due to completion of recruitment for specific BMI categories. The remaining 64 persons with MS completed the in-person session; however, one person did not have usable metabolic data based on a recording error. The final sample of 63 persons with MS were included in the data analysis.

Outcome Measures

Demographic and clinical characteristics. Participants completed a demographic and clinical characteristics questionnaire regarding age, sex, race, MS type, disease duration, and disability status based on the Patient Determined Disease Steps (PDDS). Neurological status was assessed using the Expanded Disability Status Scale (EDSS),[16] a clini-

cally-administered examination conducted by a research team member who is a Neurostatus-certified assessor.

Indirect Calorimetry for Cw. O_2 consumption (VO_2) was measured during a 5-minute seated rest and 6-minute over-ground walking bout. VO_2 was measured using a portable, indirect calorimetry system (K5, COSMED, Rome, Italy).[17] We calibrated the spirometer and gas analyzers for the calorimetry system, as per manufacturer's recommendations. We measured VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) for an estimate of resting energy expenditure, expressed as the average of two, 30-second values over the last minute of an initial five-minute period of seated rest (i.e., resting-state VO_2). Participants then performed the walking bout in the open space of the exercise testing laboratory with the instructions of walking at a normal, comfortable pace for six minutes[18] while wearing the portable calorimetry system for VO_2 measurement over the duration of the six-minute walking bout. We measured distance walked using a calibrated measuring wheel (Stanley MW50, New Briton, CT) for step length (cm). We measured net steady-state VO_2 as the difference between average VO_2 during the last three minutes of the walking bout (i.e., steady-state VO_2) and average resting-state VO_2 values;[7] this controlled for any influences of factors such as physical activity and food intake on energy expenditure. C_w was expressed as $ml \cdot kg^{-1} \cdot m^{-1}$ by dividing net steady-state VO_2 in $ml \cdot kg^{-1} \cdot min^{-1}$ by actual walking speed in $m \cdot min^{-1}$ (C_w = (Steady-state VO_2 – resting VO_2) / speed); we operationalized steady-state VO_2 as the last three minutes of the walking bout based on previous research on oxygen kinetics during a six-minute walking bout in MS.[6] We recorded steps taken during the walk using a hand-tally counter for measuring cadence (steps/min), and determining stride length based on distance traveled divided by steps taken (distance/step).

Body Composition. Height and weight were measured using a Detecto calibrated scale and stadiometer. Height and weight were used to calculate BMI with the following formula: BMI = weight (kg) / height (m^2). Body composition values were derived from the whole-body DXA scan while the participant lied on the examination table as per the manufacturer's guidelines. A GE Lunar Prodigy Primo DXA scanner (GE Healthcare, Wisconsin, USA) was used to assess soft tissue and bone composition for the whole body. Outcomes of interest were percent body fat percentage, fat mass, fat-free mass, and bone mineral content and density.

Fatigue. Perceived fatigue was measured using the Fatigue Severity Scale (FSS).[19] The FSS has nine items that are rated on a seven-point scale of 1 (strongly disagree) and 7 (strongly agree) regarding a person's severity of fatigue symptoms during the past week. The item scores were averaged for generating a measure of fatigue severity that ranges between 1 and 7. FSS scores of 4 or above are indicative of severe MS-related fatigue. There is evidence for the internal consistency, test-retest reliability, and validity of FSS scores as a measure of MS-related fatigue.[19]

Pain. Pain was measured using the short form of the McGill Pain Questionnaire (SF-MPQ).[20] The SF-MPQ contains a15-item adjective checklist that assessed sensory (e.g., "stabbing," "sharp") and affective (e.g., "sickening," "tiring-exhausting") dimensions of typical whole-body pain intensity. The items are rated using a four-point intensity scale of 0 (none) and 3 (severe), and item scores were summed for yielding an overall measure of pain severity during the previous week. Scores range between 0 and 45, and higher scores are indicative of more intense overall pain. There is evidence of internal consistency and score validity of the SF-MPQ in MS.[20]

Anxiety and Depression. The Hospital Anxiety and Depression Scale (HADS) contains 14 items that measured perceived symptoms of anxiety and depression over the past 4 weeks.[21] The items are rated on a 4-point scale ranging from 0 (most of the time) and 3 (not at all). After reverse-scoring a subset of items, the scores from the seven items per subscale were summed into total scores that ranged between 0 and 21; higher scores are reflective of a greater frequency of anxiety and depressive symptoms. Scores of 8-10 are indicative of possible anxiety or depression, whereas scores higher than 10 reflect probable anxiety or depression.[22] The scale has evidence of score reliability and validity in MS.[21]

Quality of Life. Health-related quality of life (HRQOL) was measured using the Multiple Sclerosis Impact Scale (MSIS).[23] The MSIS is a disease-specific measure of the physical and psychological aspects of HRQOL. The items are rated on a five-point scale of 1 (not at all) and 5 (extremely), and item scores were summed into subscales of physical and psychological domains of HRQOL. The physical domain was scored by summing the scores for items 1 to 20, subtracting 20, dividing the difference by 80, and then multiplying the result by 100. The psychological domain was scored by summing the scores for items 21 to 29, subtracting nine, dividing the difference by 36, and then multiplying by 100. Higher scores on both subscales represent greater impact of MS on HRQOL during the past two weeks. There is evidence for reliability and validity of the MSIS in samples with MS.[23, 24]

Spasticity. Spasticity of the ankle plantarflexors of both legs were measured by a physical therapist using the modified Ashworth scale (MAS). The MAS provides a measure of muscle hypertonia on a five-point scale, ranging from 0 (no increase in muscle

tone) through 4 (fixed muscle contracture).[25] The MAS scores for plantarflexors of both legs were averaged for the data analysis; this is based on providing a global measure of spasticity of the plantarflexors.

Sedentary Behavior and Physical Activity. The ActiGraph model GT3X+ accelerometer provided a device-measurement of sedentary behavior and physical activity. The accelerometer was initialized to collect raw data (g force) at a sampling rate of 100Hz until battery depletion. Participants wore the accelerometer on an elastic belt worn around the waist above the non-dominant hip during waking hours, except while showering, bathing, and swimming, for a 7-day period and completed a daily log. This daily log was inspected for verifying the days of wear time during processing of the data. We compared this with the log for verification. The raw accelerometer data were downloaded with the ActiLife software, reintegrated into activity counts in one-minute epochs with the low frequency extension, and then scored for minute-by-minute activity counts for time spent in sedentary behavior, light physical activity (LPA), and moderate-to-vigorous physical activity (MVPA) per day.[26] We considered a day as valid if there is a minimum of 10 hours of total wear time without continuous zeros exceeding 30 minutes, and participants with 1 or more valid days of data included in the analyses. The outcomes of interest were time spent in sedentary behavior, LPA, and MVPA. The Godin Leisure-Time Exercise Questionnaire (GLTEQ) was used as a self-report measure of physical activity.[27, 28] Participants were asked to record the number of bouts greater than 15 minutes in duration of light, moderate, and strenuous physical activity engaged in over a 7-day period. The score was calculated by multiplying the number of 15-minute bouts of light, moderate, and strenuous physical activity by weights of 3, 5, and 9, respectively,

and then summed into a total score where higher scores indicated higher engagement of physical activity.

Procedure

This study adopted a cross-sectional design, and we obtained ethical approval to undertake this study from a University, Institutional Review Board. All participants provided signed informed consent. Participants provided demographic and clinical information, underwent the EDSS, spasticity assessment, and a whole-body DXA scan, and completed the battery of questionnaires. Upon completion of the questionnaires, participants performed a six-minute walk while wearing the portable, indirect calorimetry system to assess the C_w. The order of assessments per testing session was intentionally standardized to minimize physical fatigue. Participants were given an accelerometer and belt as well as a log to measure physical activity and sedentary behavior and instructed on wearing the accelerometer for a 7-day period. Materials were sent back using a pre-addressed and pre-stamped envelope for return service via the United States Postal Service. Participants received remuneration for their time.

Data Analyses

All data were analyzed using SPSS ver. 28.0. Descriptive statistics were used to summarize demographic and clinical characteristics, as well as main study outcomes of C_w, body composition outcomes, scores of FSS, SF-MPQ, HADS, and MSIS, levels of sedentary behavior and physical activity, gait parameters, and spasticity of the sample. Values were presented as mean (standard deviation, SD), unless otherwise specified.

Spearman's rank-order bivariate correlations (r_s) were conducted to provide an indication of the relationship among the C_w, body composition outcomes, scores of FSS, SF-MPQ, HADS, MSIS, PDDS, and EDSS, sedentary behavior, physical activity, gait parameters, and spasticity of the sample in the case of for potential outliers and/or non-normal data. When covariates (i.e., variables associated with both C_w and body composition metrics) were present in the initial bivariate correlations analysis, we conducted partial Spearman's correlations controlling for those variables. The magnitude of correlation coefficients of 0.1, 0.3, and 0.5 were expressed as small, moderate, and large, respectively.[29]

RESULTS

The demographic and clinical characteristics of 63 participants with MS are presented in Table 1. The mean(SD) age of the overall sample was 46.7(11.1) years, and the sample consisted mostly of females (73%) and persons with relapsing-remitting MS (91%). The mean disease duration was 12.2(7.1) years with median PDDS and EDSS scores of 1 and 3.0 indicating mild walking disability. Mean height and weight were 166.4(11.0) cm and 80.3(18.6) kg, respectively, yielding a mean BMI of 28.7(6.3).

Table 1. Demographic and clinical characteristics of the sample of 63 persons with multiple sclerosis.

Characteristic	**Statistic**
Age, *years*	46.6(11.1)
Sex, *female:male*	46:17
MS type	
Relapsing-remitting	58
Progressive	5
Disease duration, *years*	12.2(7.1)
Disability status	
PDDS	1(3)
EDSS	3.0(2.0)
Height, *cm*	166.4(11.0)
Weight, *kg*	80.3(18.6)
BMI, kg/m^2	28.7(6.3)

Note: MS = multiple sclerosis; PDDS = Patient Determined Disease Steps; EDSS = Expanded Disability Status Scale; BMI = body mass index. Values are presented as mean(SD) unless otherwise noted. PDDS and EDSS scores are presented as median(IQR).

C_w, body composition metrics, and disease-related outcomes of the sample are presented in Table 2; Figure 1 presents VO_2 in 30-second averages across the six-minute walk and indicates steady-state occurred at 180 seconds (i.e., 3 minutes). The mean value of C_w in our sample was 0.21(0.11) $ml \cdot kg^{-1} \cdot min^{-1}$, and was comparable with values reported by previous studies.[8, 9] Regarding body composition outcomes, values of percent body fat, fat mass, fat-free mass, and bone mineral content and density were consistent with previous research examining DXA-based body composition metrics in persons with MS.[30, 31]

Table 2. Oxygen cost of walking, body composition metrics, and disease-related outcomes in the sample of 63 persons with multiple sclerosis.

Variable	**Mean(SD)**
O_2 cost, $mL \cdot kg^{-1} \cdot m^{-1}$	0.21(0.11)
BF, *%*	37.4(11.0)
FM, *kg*	30.8(13.0)
FFM, *kg*	46.4(8.8)
BMC, *kg*	2.5(0.4)
BMD, g/cm^2	1.2(0.2)
FSS	3.9(1.6)
SF-MPQ	6.0(6.5)
HADS-D	4.9(4.2)
HADS-A	6.0(4.1)
Physical MSIS	21.5(20.0)
Psych MSIS	24.8(22.8)
GLTEQ	32.6(24.2)
LPA, *min/day*	286.9(83.0)
MVPA, *min/day*	25.2(22.2)
Sedentary, *min/day*	508.5(98.8)
Step length, *cm*	62.9(14.7)
Cadence, *steps/min*	102.4(17.0)
MAS	0.1(0.3)

Note: O_2 = oxygen; BF = percent body fat; FM = fat mass; FFM = fat-free mass; BMC = bone mineral content; BMD = bone mineral density; FSS = Fatigue Severity Scale; SF-MPQ = McGill Pain Questionnaire; HADS-D = Hospital Anxiety Depression Scale – Depression; HADS-A = Hospital Anxiety Depression Scale – Anxiety; Phys = physical; MSIS = Multiple Sclerosis Impact Scale; Psych = psychological; GLTEQ = Godin Leisure-Time Exercise Questionnaire; LPA = light physical activity; MVPA = moderate-to-vigorous physical activity; MAS = Modified Ashworth Scale.

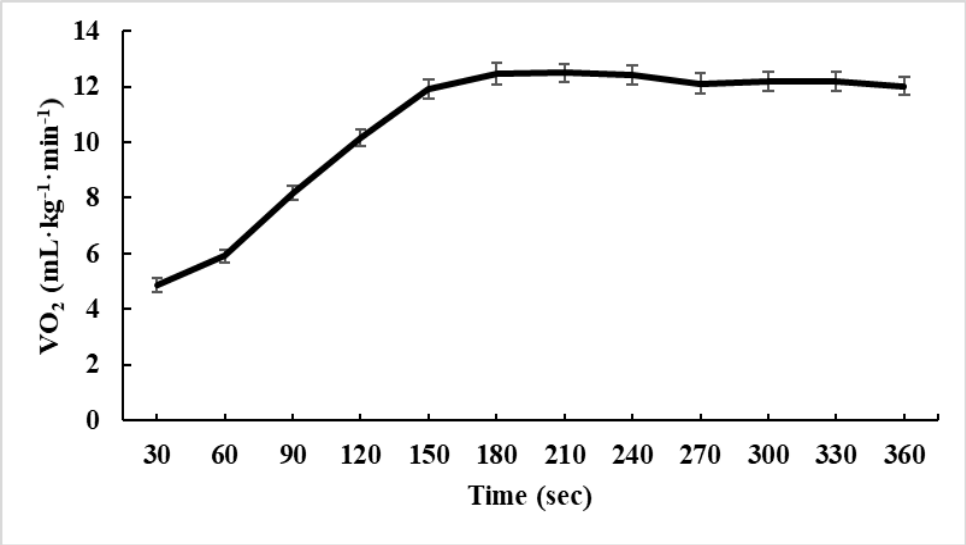

Figure 1. Oxygen consumption (VO_2) over a 6-minute walk in the sample of 63 persons with multiple sclerosis.

Spearman's rank-order correlations among C_w, body composition metrics, and disease-related outcomes in the sample of 63 persons with MS are presented in Table 3. C_w had small-to-moderate associations with body fat percentage (r_s=–.26), fat mass (r_s=–.32), and bone mineral density (r_s=–.31). C_w was further associated with the physical domain of HRQOL (r_s=–.31), step length (r_s=–.40), cadence (r_s=–.38), PDDS score (r_s=.35), and EDSS score (r_s=.44). There were no other associations between C_w and other body composition metrics or other MS-related outcomes.

Table 3. Spearman's rank-order correlations among oxygen cost of walking, body composition metrics, and disease-related outcomes in the sample of 63 persons with multiple sclerosis.

	Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1	O_2 Cost	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
2	BF	-.26*	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
3	FM	-.32*	.89	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
4	FFM	-.09	-.15	.26*	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
5	BMC	-.14	-.17	.19	.85*		--	--	--	--	--	--	--	--	--	--	--	--	--
6	BMD	-.31*	.20	.42*	.49*	.70*	--	--	--	--	--	--	--	--	--	--	--	--	--
7	FSS	.02	<.01	-.02	-.07	-.07	-.11	--	--	--	--	--	--	--	--	--	--	--	--
8	SF-MPQ	-.06	.20	.19	-.05	-.06	.06	.57*	--	--	--	--	--	--	--	--	--	--	--
9	HADS-D	.17	-.09	-.09	.02	.02	.05	.39*	.47*	--	--	--	--	--	--	--	--	--	--
10	HADS-A	-.09	.18	.07	-.20	-.22	-.04	.55*	.69*	.42*	--	--	--	--	--	--	--	--	--
11	Phys MSIS	.31*	-.09	-.08	.05	.01	-.06	.68*	.68*	.51*	.54*	--	--	--	--	--	--	--	--
12	Psych MSIS	-.09	.07	.06	.02	<.01	.09	.64*	.80*	.52*	.80*	.73*	--	--	--	--	--	--	--
13	GLTEQ	-.14	-.27*	-.24	.01	.05	-.16	-.07	-.17	-.33*	-.20	-.24	.08	--	--	--	--	--	--
14	LPA	-.09	.09	-.03	-.10	.01	-.10	.05	.03	-.14	.14	-.03	-.11	.20	--	--	--	--	--
15	MVPA	-.20	-.05	-.05	<.01	-.02	.12	-.23	-.17	-.32*	-.08	-.28*	<.01	.42*	.38*	--	--	--	--
16	Sedentary	.11	-.27*	-.21	.11	.06	-.20	-.09	-.35*	-.18	-.27	-.09	-.31*	.02	-.60*	-.17	--	--	--
17	Step length	-.40*	-.22	-.09	.23	.30*	.12	-.20	-.16	-.25*	.03	-.38*	-.09	.37*	.16	.47*	.11	--	--
18	Cadence	-.38*	.11	.06	-.15	-.07	-.03	.00	.04	-.17	.01	-.23	-.05	.28*	.18	.24	-.04	.33*	--
19	MAS	.24	-.06	-.05	-.03	-.17	-.23	.14	.18	.12	.11	.29*	.13	<.01	<.01	-.17	-.01	-.23	-.24

Note: O_2 = oxygen; BF = percent body fat; FM = fat mass; FFM = fat-free mass; BMC = bone mineral content; BMD = bone mineral density; FSS = Fatigue Severity Scale; SF-MPQ = McGill Pain Questionnaire; HADS-D = Hospital Anxiety Depression Scale – Depression; HADS-A = Hospital Anxiety Depression Scale – Anxiety; Phys = physical; MSIS = Multiple Sclerosis Impact Scale; Psych = psychological; GLTEQ = Godin Leisure-Time Exercise Questionnaire; LPA = light physical activity; MVPA = moderate-to-vigorous physical activity; MAS = Modified Ashworth Scale. *p<0.05.

Body fat percentage was further associated with self-reported physical activity (r_s=–.27) and time spent in sedentary behavior (r_s=–.27). BMI was also significantly associated with self-reported physical activity (r_s=–.27) and sedentary behavior (r_s=–.26). However, FFM and BMD were not associated with any other variables including scores of FSS, SF-MPQ, HADS, and MSIS as well as device-measured physical activity, gait parameters or spasticity.

DISCUSSION

This study examined C_w and its association with body composition and other disease-related outcomes in persons with MS. The bivariate correlation analysis indicated that higher C_w was significantly associated with lower body fat percentage, total fat mass, and BMD. Higher C_w was further associated with higher disability status, slower cadence, shorter step length, and worse physical MS-specific HRQOL. Such preliminary results might support the design of interventions that focus on the optimization of body composition (i.e., reducing fat mass, increasing bone mineral density) or gait profiles for managing C_w and its effects on other consequences such as disability and physical well-being in MS.

There is evidence that C_w is elevated in persons with MS, and we examined body composition outcomes as potential factors influencing C_w. To date, this is the first study to examine the relationship between body composition outcomes using DXA and the C_w in persons with MS. Some researchers examined this relationship using BMI in persons with MS and reported a moderate effect size for the difference in C_w between persons of the normal and obese categories, in that persons of the obese category had lower C_w than

persons in the normal weight category; however, there was no significant difference between the two groups.[13] Our results replicated their findings, in that BMI was not associated with C_w in our sample. One possible explanation may be that persons with more adiposity use adaptative mechanisms to minimize energy expenditure while walking at preferred speeds, a strategy that non-obese persons also use.[32] We extended that research by using DXA for body composition outcomes, rather than just BMI, for the differentiation between fat mass, fat-free mass, and bone mineral content and recruited persons with a wide range of body composition profiles. Our results indicated that lower percent body fat was associated with higher C_w in our sample of persons with MS. More research is warranted to better understand underlying mechanisms (i.e, biomechanical, physiological) that account for the relationship between lower percent body fat and higher C_w in this population. The results further indicated that lower BMD was associated with higher C_w.

C_w was associated with higher PDDS and EDSS scores, slower cadence and shorter step length in our sample of persons with MS. This is consistent with previous research that has identified disability status and those two gait parameters as significant correlates of C_w in persons with MS.[8-10] We expected that persons with higher disability status would experience greater abnormalities in gait and, therefore, a higher C_w. Based on the results of previous and current research, the findings support the design of interventions that target gait training in persons with MS, especially for persons with more severe disability, as an approach for reducing C_w and manage its consequences.[8-10]

Our results further indicated that persons with MS who had higher C_w reported worse MS-specific impact on the physical domain of HRQOL. This suggests that persons with MS who expend more energy while walking may perceive worse day-to-day physi-

cal well-being because of energetic inefficiency during a primary physical task of the day. A potential avenue of research may consider examining HRQOL as an outcome of interventions that target management of C_w in persons with MS.

Of note, there were no associations between body composition metrics and MS-related outcomes of fatigue, pain, depression, and anxiety in our sample of persons with MS who had a wide range of body composition profiles (i.e., normal weight, overweight, and obese categories based on BMI). This is consistent with previous research that examined the relationship between body composition outcomes and symptoms (i.e., fatigue, depression, anxiety, pain, sleep quality) in physically inactive persons with MS.[30] There may be underlying factors other than body composition outcomes that explain the manifestation of symptoms (i.e., fatigue, pain, anxiety, depressive symptoms) and worse HRQOL in persons with MS. Moreover, previous research reported no relationship between BMI and gait parameters,[13] and our research replicated those results, in that both BMI and body fat percentage were not associated with cadence or step length. Our findings suggest that having a worse body composition profile is not necessarily related to poor disease-related outcomes or vice versa. However, behavioral interventions with the aim to optimize body composition outcomes in MS may target increasing overall physical activity, as higher body fat percentage and BMI were associated with lower self-reported physical activity in our sample of persons with MS. Participation in physical activity, especially exercise, may further yield other benefits in MS.[32, 33] Although body fat percentage and BMI were negatively associated with sedentary behavior, reducing excess body fat and sedentary behavior should still be considered as targeted approaches to manage health-related outcomes such as blood pressure in persons with MS.[34]

There are limitations to consider when interpreting the results. The study involved a cross-sectional design, and this precluded inferences regarding causality. A limitation is the lack of control of additional factors that may influence metabolic processes or walking such as diet, medication, sleep quality, smoking, or mitochondria capacity and function. Another limitation is that our protocol did not measure C_w across various speeds (i.e., slower, faster). Persons with different body composition profiles may adjust their energy efficiency accordingly when walking at different speeds. One other limitation is that this study's recruitment and data collection took place amid the COVID-19 pandemic, and the effects of this pandemic may have contributed to these symptoms and domains of quality of life.

Overall, the study indicated that higher C_w was associated with lower percent body fat and BMD. The presence of higher C_w was associated with higher disability status, slower cadence, reduced step length, and worse physical HRQOL. Of note, there was no relationship between other body composition outcomes and symptoms of MS; however, higher body fat percentage and BMI were associated with lower sedentary behavior and self-reported physical activity. Future research may focus on interventions for optimizing body composition (i.e., reducing fat mass, increasing bone mineral density) as a possible approach for changing C_w and, in turn, its consequences such as disability in MS.

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SUMMARY

C_w is a physiological indicator of energy required for movement and may reflect contributions of gait abnormalities and other disease manifestations such as spasticity.[3] Previous research demonstrated higher C_w in persons with MS compared to controls matched by age and sex and worse C_w as a function of increasing disability status and spasticity.[2, 4] This is seemingly accounted for by gait parameters such as cadence and stride length. However, there is limited evidence of other correlates, predictors, and approaches for management of elevated C_w in this population.

This line of research further examined the C_w in persons with MS for informing future research for its management. The first project provided a review of existing research about the C_w in MS, its correlates, predictors, and consequences, and approaches for management.[6] The review further identified limitations and potential avenues for research in the C_w in MS. The second project identified peak aerobic power and mediolateral sway as modifiable correlates of higher C_w.[7] The results of this study can inform future research in the examination of high-intensity interval training and/or postural control training as an approach for increasing aerobic capacity and improving postural control to manage elevated C_w in MS. The third project reported that spasticity of the ankle plantarflexors was a significant correlate C_w and that gait parameters, particularly cadence and step length, account for this relationship between worse spasticity and elevated C_w.[8] This supports the design of future interventions to manage spasticity for reducing C_w and its consequences. The last project indicated that higher C_w was associated with lower percent

body fat and bone mineral density. Elevated C_w was further associated with higher disability status, slower cadence, shorter step length, and worse physical health-related quality of life. Such results might support the design of interventions that focus on the optimization of body composition profiles to manage C_w and its consequences such as physical well-being. However, further research on underlying mechanisms is warranted to explain the inverse relationship between body composition metrics and C_w in persons with MS.

In summary, we have identified several correlates, predictors, and consequences of elevated C_w including peak aerobic power, mediolateral sway, spasticity, gait parameters, body composition outcomes, and physical well-being. To date, there are few targeted approaches for managing C_w and changing its consequences in persons with MS. The findings of this research suggest that researchers, clinicians, and exercise specialists may focus on targeted interventions (i.e., exercise, gait rehabilitation, body composition optimization) for the management of C_w and, in turn, its consequences such as disability and quality of life.

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APPENDIX

IRB APPROVAL LETTER

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 |
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APPROVAL LETTER

TO: Jeng, Brenda

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

DATE: 04-Mar-2022

RE: IRB-300004136
IRB-300004136-017
Body Composition and Oxygen Cost of Walking in Persons with Multiple Sclerosis

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The IRB reviewed and approved the Continuing Review submitted on 21-Feb-2022 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Determination: Approved
Approval Date: 04-Mar-2022
Approval Period: One Year
Expiration Date: 18-Jan-2023

Please note:

- The IRB reviewed the Serious Adverse Events and Unanticipated Problems submitted in the Continuing Review smart form.

Documents Included in Review:

- cf.clean.211122

- CONTINUING REVIEW EFORM

To access stamped consent/assent forms (full and expedited protocols only) and/or other approved documents:
1. Open your protocol in IRAP.
2. On the Submissions page, open the submission corresponding to this approval letter. NOTE: The Determination for the submission will be "Approved."
3. In the list of documents, select and download the desired approved documents. The stamped consent/assent form(s) will be listed with a category of Consent/Assent Document (CF, AF, Info Sheet, Phone Script, etc.)