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The relationship between sleep quality and gait in people with multiple sclerosis: A pilot study

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Background: Gait deficits are common among people with multiple sclerosis (PwMS). Therefore, investigating factors that may influence walking in PwMS is important. Previous studies in older adults and other neurological populations demonstrated the relationship between sleep quality and gait performance. Despite the fact that the prevalence of poor sleep quality is very high among PwMS, little is known about the effect of sleep quality on gait among PwMS.
Objective: This study aimed to explore the relationship between sleep quality and gait performance in PwMS.
Methods: Forty-one PwMS participated in the study between February 2019 and December 2019. Participants were asked to walk at a self-selected speed over 10 m with an inertial measurement unit (IMU) attached over the back. Walking speed, step length (left and right), and step time were calculated. Sleep was estimated objectively using a wrist-worn triaxle-accelerometer; the derived parameters were sleep efficiency (SE) and the number of awakening after sleep onset (NASO).
Results: SE significantly correlated with step length ($p = 0.02$). Furthermore, the NASO significantly correlated with gait speed ($p = 0.03$), and step-time ($p = 0.02$). These correlations remained significant even after adjusting for age and disease duration.
Conclusion: We observed that when corrected for disease duration and age there were relationships between NASO and SE to gait parameters; these observations warrant further investigations.

Keywords: Multiple sclerosis; gait; sleep quality.

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Introduction

Eighty-nine percent of people with Multiple Sclerosis (PwMS) report walking as a primary limitation.[1] Deficits in gait in this population occur early in the disease process and typically worsen with the disease progression.[2–4] PwMS including those with minimal disability (i.e., Expanded Disability Status Scale (EDSS) scores ≤ 3.5) demonstrated decreased walking speed, reduced step time and length, and increased time in double support when compared with healthy controls.[3–5] Gait deterioration in this population leads to increased risk of falls,[6] loss of independence, and a significant reduction in quality of life.[7]

Deficits in gait in this population are most likely to be multifactorial. Factors such as muscle weakness, balance problems, spasticity, fatigue and cognitive deficits have been found to impact gait performance in PwMS.[8–10] In addition to these factors, few studies in older adults and in other neurological populations have reported that reduced sleep quality can be a contributing factor to gait deficits.[11,12] For example, a recent study in older adults found that lower sleep efficiency (SE) was associated with decreased gait speed and increased gait variability.[13] This phenomenon was further confirmed in individuals with Parkinson's Disease and stroke survivors.[11,12] In PD, sleep disorders such as rapid eye movement sleep behavior disorder (RBD) were also found to be highly correlated with the increase in gait impairments such as freezing episodes.[14] The exact process of how sleep quality may affect gait performance in these populations is still not clear. However, this observation can be traced back to a number of reasons. For example, studies have reported that poor sleep quality is associated with cognitive impairments in elderly individuals and neurological populations such as stroke and PD.[15–18] Taking into consideration that gait is a complex skill that requires spatial and temporal integration of sensory input, motor planning and cognitive function, poor sleep quality might therefore, reduces these functions and consequently affects gait function. Poor sleep quality is associated with deterioration in executive functions, and motor control which in turn may worsen gait performance.[19] Interestingly, in stroke population, Moon *et al.*, have linked gait impairments to impaired "sleep-dependent motor learning" process.[12] During rehabilitation, motor learning in gait is achieved through goal-directed repetitive exercises, and evidence is growing that sleep may be important for consolidating and improving learning of all skilled actions including gait.[20]

Sleep disturbances are highly prevalent in PwMS. Approximately, 70% of PwMS experience sleep problems.[22–25] Insomnia,[25] restless leg syndrome (RLS),[26] RBD,[27,28] and sleep apnea[23] are common among PwMS. Aetiology of sleep deficits in this population still remains unknown. However,

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studies indicated that sleep disorders during the course of MS can be secondary to several disease-specific symptoms including, depression, fatigue, spasticity, pain and medication-side effects.[29,30] In addition, sleep disorders in PwMS can be primary with a common biological link. For example, circadian rhythm disorders and increased levels of pro-inflammatory cytokines have been recognized as potential factors in affecting sleep homeostasis in PwMS. Furthermore, lesion load was also linked to sleep disturbances in PwMS.[31]

Overall, although sleep disturbances are common in PwMS, no study has investigated the relationship between sleep quality and gait parameters in PwMS. Therefore, the main aim of this study was to explore the relationship between gait performance and sleep quality in PwMS. We hypothesized that sleep quality is correlated with gait performance in PwMS. The relationship between sleep quality and gait performance in this population can be traced back to structural and functional overlap in networks controlling both sleep and gait. In particular, the degeneration in the pedunculopontine nucleus (PPN) in PwMS[32] can potentially contribute to poor sleep quality as well as gait deficits at the same time.[33] The pedunculopontine nucleus (PPN) has a nonmotor function in modulating the sleep cycle (wakefulness and sleep)[34]; the PPN activates the cerebral cortex to maintain wakefulness.[34] At the same time, the PPN is considered a pivotal station for gait and postural control, in which it links the brainstem, cortex, basal ganglia and the spinal cord. Accordingly, lesions in PPN might lead to disturbances in sleep and gait at the same time.[35] Furthermore, as we indicated earlier, evidence suggests that poor sleep quality leads to cognitive decline.[36] Within this realm, it should be noted that in PwMS, gait is characterized by greater reliance on executive control, which requires more cognitive resources.[6] Therefore, we believe that deterioration in sleep quality in people with MS may affect gait due to the decline in the executive skills.[33]

Understanding the relationship between sleep and gait might have important implications for clinicians who work with PwMS. Studying factors associated with gait in PwMS may pave the way for strategies for better gait rehabilitation in this population. In particular, findings of this study would give attention to consider sleep quality as an important factor to be included in rehabilitation intervention to improve gait outcomes in PwMS.

Methods

Study design and participants

A cross-sectional study was designed to examine the relationship between sleep characteristics and gait performance in PwMS. Patients attending routine neurology clinic appointments at King Abdulla University Hospital (Irbid, Jordan) were screened for eligibility by a neurology consultant. Inclusion criteria were as follows: (1) age above 18 years, (2) the capacity to give informed consent, (3) the capability to independently walk with or without using walking aids. Exclusion criteria were as follows: (1) the existence of another neurological disease that may affect balance and gait (e.g., stroke, TBI), (2) the existence of severe behavioral disorders or communication difficulties as determined by the neurologist, (3) for females: being pregnant. All participants gave written informed consent approved by the Institutional Research Committees of the Jordan University of Science and Technology (AA- 20190214).

Study procedure

Each participant was asked to visit the physiotherapy laboratory at Jordan Science and Technology University (JUST) for a single assessment session. The session started with collection of basic personal and demographic information (age, gender, height, weight, and shoe size). In addition the Expanded Disability Status Scale (EDSS) was completed.[37] Participants were asked to perform the walking of a self-selected speed over 10 m. Furthermore, participants were asked to wear an Actisleep (ActiGraph; Pensacola, FL) device a week before the testing session to objectively asses sleep quality (see details below).

Evaluation of gait

Participants were asked to walk over a 10 m distance, obstacle-free flat surface, at their self-selected walking pace. An inertial measurement unit (IMU) (LPMS-B, Life Performance Research, Japan) was attached, using double adhesive tape, to the fourth lumbar area to track the projected center of mass.[6] Acceleration in the object frame was transposed to the global frame using a quaternion rotation matrix, and double integrated to get accurate vertical Center of Mass (CoM) displacement.[38] Gait parameters were derived using a

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validated inverted pendulum methodology, resulting in validated walking speed, step length (right and left) and step time.[39] In brief, gait characteristics were derived using inverted pendulum mechanics,[40] whereby the center of mass (CoM) vertical excursion was related to individual step lengths. However, instead of using a typical correction factor of 25%, to counter the forward displacement made during the double stance phase, we added 75% of the participant's foot length to their pendulum-derived step length to get a validated outcome of overall step and stride length.[41,42] In order to obtain foot-length data, shoe size was used assuming a good fit of shoe-wear which in turn was converted to foot length.

Evaluation of sleep characteristics

The sleep characteristics were assessed objectively using Actisleep (Actigraph wGT3X-BT, Pensacola, Florida, USA). Actisleep[43] is a tri-accelerometer that measures sleep/awake positions. Actisleep was found to be a valid and reliable device for sleep measurements when worn at wrists in healthy young adults.[44] The clinical utility for using the Actisleep in PwMS has been demonstrated in several studies.[45–47] In addition, Actisleep was found to correlate with subjective report of sleep quality and it is sensitive to detect compromised or altered sleep patterns in disordered neurological populations.[48]

In this study, participants were asked to wear the Actisleep for 7 consecutive days (24 h/day) on the non-dominant wrist.[49] Participants received detailed information on how to wear the accelerometer and were asked to remove it only for water activities like swimming or showering. Participants were asked to behave naturally and habitually during the wearing time. Data from Actisleep were analyzed using Actilife software (ActiGraph, version xx; Pensacola, FL).[43] Actisleep signals were sampled with 30 Hz. Only days with more than 10 h wear time were included in the analysis. We included 4 days of more than 10 h wear time for each participant. Non-wear periods were excluded from the analysis. The inclusion of at least 4 days of 10 h wear time was recommended to assure quality of the data.[50] The derived parameters from the Actisleep included sleep efficiency (SE) and the number of awakening after sleep onset (NOSA). SE represents the number of sleep minutes divided by the total minutes the participant was in bed. Better sleep quality is associated with higher SE; overall, SE $\geq$ 85% is considered to be an indicative of good sleep quality.[51] Sleep efficiency and NOSA are considered important parameters of undisrupted sleep and can detect poor sleep quality.[52,53] Improvement in sleep efficiency has become a gold standard for evaluating the efficacy of different treatment interventions.[52] A certain amount of sleep continuity (i.e., undisrupted sleep) which can be reflected by the NOSA is important for health wellbeing.[54]

Statistical analysis

All data were analyzed using SPSS (Statistical Package for the Social Sciences Version 28 (SPSS, Chicago)). Demographic data were presented as frequency for categorical variables and mean $\pm$ standard deviation for continuous variables. Bivariate correlational analysis between main variables (sleep and gait parameters) was conducted using Spearman correlation coefficient (r). In general, r of > 0.50 indicates a large correlation, 0.31 to 0.49 indicates a moderate correlation, and < 0.30 indicates a poor correlation.[55]

To account for age, BMI, disease duration, and the use of disease-modifying therapies (yes/no) as potential cofounding factors, the relationship between sleep characteristics and gait parameters were examined using partial correlation analysis. Partial correlation coefficient is a coefficient to describe the relationship between two variables with the effect of a set of other variables is removed (i.e., the effect of confounding variables is removed).[56,57] These variables (i.e., age, BMI, disease duration and medication use) were considered confounding factors as age and BMI are associated with gait performance,[58,59] and age is associated with sleep quality[60] as well as with gait performance.[61] Additionally, disease duration is linked to deterioration in gait[5] and sleep[62] in PwMS. On the other hand, disease-modifying therapies (i.e., immunotherapies) are known to affect sleep in PwMS.[31] The side-effect of anti-depressant can affect both sleep quality and gait performance.[63] However, none of the participants who were included in this study was on anti-depressant, therefore the use of anti-depressant was not considered in the data analysis. An alpha level of 0.05 was used to determine the significance level.[64]

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Sample size

Power analysis for a partial correlation was conducted in SPSS (version 28) to determine a sufficient sample size. With four variables to control for, $\alpha = 0.05$, a power of 80%, two tails and a conventional large effect size ($r = 0.05$), a sample of at least 41 participants is required.

Results

Table 1 demonstrates the demographic and clinical characteristics of participants. In total 41 PwMS were recruited in this study. Their age ranged from 18 to 57 years old. The Expanded Disease Disability Scale (EDSS) ranged from 0 to 6. In addition, SE ranged from 25% to 90%, and NOSA ranged from 4 to 47.

Table 2 demonstrates the extent of the relationship between sleep characteristics and gait parameters. There was a moderate, positive, and statistically significant relationship between SE and step length ($p \leq 0.05$) (i.e., when SE increased, the step length increased (positive relationship)). Furthermore, there were moderate, negative, and statistically significant relationships between NASO and gait speed as well as step time ($p \leq 0.05$) (i.e., when NASO increased, walking speed and step time were reduced (negative relationship)). All these correlations remained significant, even after controlling for the confounding effect age, BMI, disease duration and the use of disease-modifying therapies ($p \leq 0.05$) (Table 3).

Table 1. Demographics and clinical characteristics of participants ($n = 41$).

Variables	Mean ± SD
Age (years)	34.6 ± 9.8
Weight (Kg)	66.7 ± 21.2
Height (cm)	154.3 ± 33.1
EDSS score	2.6 ± 1.4
Duration (years)	7.8 ± 5.6
Gender n (Female/Male)	24/17
Sleep efficiency (%)	71.7 ± 14.8
NOSA (n)	18.5 ± 9.2
Gait speed (m/s)	0.92 ± 0.3
Step time (LT) (ms)	528.2 ± 109.6
Step time (RT) (ms)	534.8 ± 137.3
Step length (LT) (m)	0.61 ± .07
Step length (RT) (m)	0.62 ± 0.06
Use of anti-depressant (Yes: n (%))	0 (0%)
Use of disease modifying therapies (Yes: (n (%))	24 (58.5%)

Notes: EDSS: expanded disability status scale, LT: left side, RT: right side, Kg: kilogram, n: number, m: meter, cm: centimeter, ms: millisecond.

Table 2. Spearman correlation coefficients (r) between sleep quality and gait parameters.

	NOSA	SE
Gait speed	$r = -0.35$* $p = 0.03$	$r = 0.25$ $p = 0.13$
Step time (LT)	$r = -0.13$ $p = 0.06$	$r = -0.17$ $p = 0.29$
Step time (RT)	$r = -0.37$* $p = 0.02$	$r = 0.14$ $p = 0.39$
Step length (LT)	$r = -0.27$ $p = 0.09$	$r = 0.36$* $p = 0.02$
Step length (RT)	$r = -0.17$ $p = 0.29$	$r = 0.33$* $p = 0.04$

Notes: SE: sleep efficacy, NOSA: number of awakening after sleep onset, LT: left RT: right, *$p \leq 0.05$.

Table 3. Partial correlations between sleep quality and gait parameters controlling for age, BMI, duration of disease and the use of disease-modifying therapies.

Parameters	NOSA	SE
Gait speed	$r = -0.36$* $p = 0.05$	$r = 0.30$ $p = 0.07$
Step time (RT)	$r = -0.35$* $p = 0.03$	$r = 0.06$ $p = 0.75$
Step time (LT)	$r = -0.24$* $p = 0.14$	$r = 0.17$ $p = 0.31$
Step length (RT)	$r = -0.22$ $p = 0.19$	$r = 0.39$* $p = 0.01$
Step length (LT)	$r = -0.09$ $p = 0.58$	$r = 0.39$* $p = 0.01$

Notes: SE: sleep efficacy, NOSA: number of awakening after sleep onset, LT: left, RT: right, *$p \leq 0.05$.

Discussion

To our knowledge, this is the first study that has explored the relationship between sleep quality measures and gait parameters in PwMS. The results demonstrated that sleep efficiency and NASO were significantly associated with gait parameters. These correlations of NASO and SE remained significant after adjusting for age and disease duration.

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Previous studies reported a number of factors that might have a major impact on gait performance in PwMS. Factors such as muscle weakness, balance problems, spasticity, fatigue and cognitive deficits have been found to impact gait in PwMS. Our results extend this earlier research by demonstrating that individuals' sleep quality also might be an important factor that impacts gait performance. The findings of this work are in line with previous findings conducted in healthy individuals, other neurodegenerative diseases, and stroke.[11–13,19] In Parkinson's disease it was found that poor sleep quality, indicated by poor SE and greater sleep fragmentation, is correlated significantly with step-width variability.[11] Similarly, in individuals with stroke, it was found that sleep disturbances negatively affected functional outcomes, especially balance and gait functions.[12]

Overall, the exact mechanism of how sleep may affect walking is still not fully understood. However, one possible mechanism is the degeneration observed in neuroanatomical regions in PwMS that regulate both sleep and gait, including the pontine tegmentum, and the pedunculopontine nucleus.[65] Therefore, degeneration in these areas can potentially contribute to poor sleep quality and gait deficits at the same time.[65] Furthermore, a recent study illustrates that sleep deprivation leads to a decrease in performance of sensorimotor control of gait,[19] as the basal ganglia and cerebellum are disrupted by sleep deprivation.[19,65]

Another possible mechanism is that metabolic wastes are washed during sleep.[66] The accumulation of metabolic wastes, in turn, leads to less muscles fatigue resistance, and subsequently, gait impairment.[66] For example, Lamon *et al.*[67] reported that sleep deprivation blunts skeletal muscle protein synthesis and promotes a catabolic environment. Even a single night of sleep impairment was found to be sufficient to induce anabolic resistance in the muscles.[67] Moreover, accumulation of metabolic wastes in the brain, disturb neurotransmitters production and further affect gait and motor function, as well as concentration that is needed for balance and gait.

In addition to the above, the relationship between poor sleep quality and gait deficits can be traced back to the observation that those who were sleep-deprived experienced deterioration in executive functions, and motor control which in turn may worsen gait performance.[19] Within this realm, it should be noted that in PwMS, gait is characterized by reduced automaticity and greater reliance on executive control, which require more cognitive resources.[6] Therefore, deterioration in sleep quality in people with MS may affect executive skills through its direct effect on frontal lobe activation, or through its effect on arousal and motivation mechanisms, which in turn affect executive skills and cognition.[33]

These results are of clinical importance considering the high prevalence of sleep disturbances and gait impairments in PwMS. It might be possible to improve gait performance by improving sleep quality. Strategies that target improving sleep quality could directly result in improving gait or improving other MS-related impairments which in turn impact gait performance in PwMS. For example, studies found that improving severe obstructive sleep apnea[68] through the beneficial effects of continuous positive airway pressure (CPAP) application improves gait control of severe obstructive sleep apnea patients. In our previous published work, we have demonstrated that PwMS who participated in a supervised aerobic exercise program demonstrated improvements in sleep measures.[46] Exercise may be a non-pharmacological, inexpensive, safe method to improve sleep quality in PwMS. Moreover, a recent study shed the light on how sleep quality impact the motor skill acquisition in PwMS.[45] By understanding the role of sleep, therapists can more effectively adjust the practice doses to fit the needs of their patients. Besides, in clinical settings, sleep assessment is not considered a major part of health care professional evaluation. However, due to the role the sleep might have on gait, we believe that clinicians need to assess sleep when dealing with PwMS.

The authors acknowledge some of the limitations of this study. The study was a cross-sectional design that is considered observational, leaving the issue of causality ambiguous. Although many confounding factors that might affect the relationship between sleep quality and gait performance were included in this study, some other factors that might influence this relationship such as fatigue level, cognitive impairments and level of physical activity have not been assessed. Future studies, therefore, that include these factors are needed to confirm these results. Fatigue is very prevalent in PwMS; the previous studies reported a relationship between fatigue level and sleep deficits as well as gait parameters in this population.[69,70] Furthermore, cognitive impairments are linked to both sleep quality and gait performance in PwMS.[71,72] Similarly, previous studies reported significant relationship between sleep quality and level of physical activity in PwMS.[30] Future studies that include fatigue, cognitive impairments and physical activity as confounding factors when examining the relationship between sleep quality and gait performance in PwMS are warranted.

In conclusion, our data suggest that reduced SE and NOSA are associated with decreased gait performance in PwMS. This study offers a first step towards the development of effective interventions that may simultaneously improve sleep quality and gait. We believe that it is crucial to provide healthcare professionals with recommendations to consider sleep as an important factor for improving gait.

Conflict of Interest

The authors report there are no conflict of interests to declare. The authors would like to acknowledge all the participants of the study.

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Author Contributions

Dr. Khalil contributed to concept & design, data collection & analysis, drafting the manuscript, revising the final version of the manuscript, and project management.

Dr. Al-Sharman contributed to concept & design, data collection & analysis, drafting the manuscript, and revising the final version of the manuscript.

Mrs. Abedalaziz contributed to contribute to concept & design, data collection & analysis, and drafting the manuscript.

Dr. Patrick and Professor Dawes contributed to concept & design, gait data processing, and revising the manuscript.

All other authors contributed to concept & design, and revising the manuscript.

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