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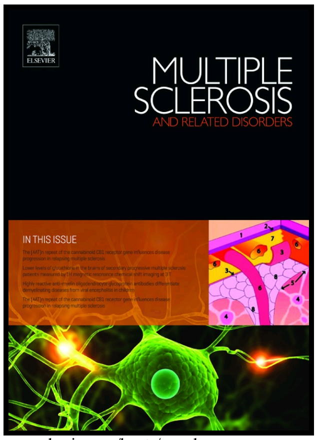

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The Association between Physical Activity and Sleep Characteristics in People with Multiple Sclerosis

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Abstract

Study objectives: The majority of individuals with multiple sclerosis (MS) suffer from sleep disorders. In this study, we investigated the relationship between physical activity and sleep characteristics in MS patients.

Methods: Sixty MS patients were recruited in the study. Sleep characteristics were assessed using the Actisleep device while physical activity levels were assessed using mobility accelerometer.

Results: The results showed that means (± SD) of sleep latency (SL) and sleep efficiency (ES) for MS patients were 23.89 ± 13.23 minutes and 87.52 ± 76.89% respectively. The participants' total time in sleep (TST) and wake after sleep onset (WASO) were 353.25 ± 63.98 minutes and 83.84 ± 42.23 minutes respectively. With respect to physical activity levels, means (± SD) of light (LA), moderate (MA), vigorous (VA) activities and moderate to vigorous physical activity (MVPA) were 11660.15 ± 18145, 212.04 ± 148.67, 9.70 ± 9.26 and 222.88 ± 154.60 counts per minute, respectively. Pearson's correlation analysis showed that WASO correlated significantly with LA, MA and MVPA ($P<0.05$). These correlations remained significant even after accounting for age, body weight and disease severity ($P<0.05$).

Conclusion: The results show a positive relationship of physical activity with sleep parameters in individuals with MS.

Keywords: sleep disturbances, sleep characteristics, physical activity, multiple sclerosis.

List of abbreviations:

MS: multiple sclerosis, SL: sleep latency, SE: sleep efficiency, TST: total sleep time, WASO: wake after sleep onset, LA: light activities, MA: moderate activities, VA: vigorous activities, EDSS: the expanded disability status scale, CPM: counts per minute, MVPA: moderate to vigorous physical activities, MET: metabolic equivalent, SD: standard deviation.

Introduction

Sleep disorders are highly prevalent in individuals with multiple sclerosis (MS)(Nagaraj et al. , 2013), as ~50% of the patients report sleep problems (Stanton et al. , 2006). Individuals with MS frequently complain from initial, middle, and terminal insomnia, daytime sleepiness and restless leg syndrome (Bamer et al. , 2008b, Boe Lunde et al. , 2012, Carnicka et al. , 2014, Pokryszko-Dragan et al. , 2013). These sleep problems are associated with nocturia, spasms, snoring, pain, site of lesion, fatigue and depression (Alarcia et al. , 2004, Clark et al. , 1992, Fleming and Pollak, 2005, Tachibana et al. , 1994). The increase in frequency and symptoms of sleep disorders in MS dampened mode, mental and physical health, and quality of life in this population(Bamer et al. , 2008a, Merlino et al. , 2009). These sleep-related manifestations underline the importance of understanding sleep problems and management in individuals with MS.

Little is known about the management of sleep disturbances in MS individuals. One study reported that about one third of individuals with MS use sleep medications 2-3 times/week, which is considerably high compared to the general population (Bamer et al. , 2010). Overall, attention toward the use of alternative therapies to improve sleep qualities is growing, including the use of exercise and physical activity in other neurodegenerative diseases. For example, in Parkinson's disease, it was found that aerobic, strengthening and Qigong exercises were associated with improvement of sleep quality (Rodrigues de Paula et al. , 2006, Wassom et al. , 2014). A more recent study found that mild-moderate intensity multimodal exercise can contribute to reducing sleep disturbances in Parkinson's disease and Alzheimer disease patients (Nascimento et al. , 2014). Results of these studies are promising and suggest that exercise could be used as an adjunct therapy for management of sleep disturbances and improving quality of life in people with neurological diseases. As yet, the effect of exercise on sleep is not fully understood in MS. Using exercise for sleep problems could help decreasing the side effects of sleep medications such as dependency and drowsiness (Harvey et al. , 2012). In the general population, increased participation in physical activities has been reported to improve sleep quality and quantity (Kim et al. , 2000, Liu et al. , 2000, Morgan, 2003,Ohida et al. , 2001). Physically active people reported less awakenings after sleep onset (WASO), shorter sleep latency (SL) and less daytime sleepiness (Andreasen et al. , 2011). On the other hand, sleep disturbances have been found to be related to less physical activity in the general population (Motl and Gosney, 2008, Motl et al. , 2005) and mobility limitations in the elderly(Stenholm et al. , 2010). Furthermore, sleep disturbances have been also reported to predict future physical inactivity (Stenholm, Kronholm, 2010).

Individuals with MS are less physically active than the general population(Motl, McAuley, 2005). Several factors including fatigue, muscle weakness, and poor coordination, can contribute to the decreased physical activity in this population (Stuifbergen and Becker, 2001).This reduction in physical activity may contribute to sleep disturbances in individuals with MS. However, this relationship is not known in MS individuals yet as only one study examined the relationship between physical activity levels and day-time sleepiness in individuals with MS, but not sleep characteristics (Merkelbach et al. , 2011). Thus, further studies are required in the area of physical activity and sleep in individuals with MS. This area is particularly important as it could help improve health status in individuals with MS and shed the light into potential therapeutic options.

The aim of this study was to determine whether sleep measures, including total sleep time, wakening after sleep onset (time of wake in minutes after sleep onset), sleep efficiency (total sleep time in minutes divided by total time spent in bed in minutes) and sleep latency (time in minutes needed to fall asleep) are associated with different levels of physical activities in MS individuals. These sleep characteristics were chosen as they are proven to reflect sleep quality and relates to quality of life in health and disease (Sadeh, 2011). It was hypothesized that less total sleep time (TST), poorer sleep efficiency (SE), greater awakening after sleep onset would be associated with lower levels of physical activity in MS individuals.

Methods

2.1. Study Design and Subjects

A cross-sectional study was designed to examine the relationship between physical activity levels and sleep characteristics in individuals with MS. Sequential MS participants attending routine neurology clinic appointments at King Abdulla University Hospital and Jordanian Multiple Sclerosis Society were screened for eligibility by a neurology consultant. Inclusion criteria were: 1) relapsing-remitting MS, 2) no exacerbation of symptoms 30 days prior to the testing day, 3) age above 18 years and 4) the capacity to give informed consent (Melamud et al. , 2012). Exclusion criteria were: 1) participants who had received steroid treatment less than one month prior to enrollment, 2) women who were pregnant, 3) lactating or taking oral contraceptives, 4) participants with other endocrine or immune disorders, 5) participants on sleep medication or having other neurological diseases(Melamud, Golan, 2012). Participants provided informed consent in accordance with the ethical approval obtained from the Institutional Research Board of King Abdulla University Hospital (HK-2014194). Disease severity was assessed using the expanded disability status scale (EDSS)(Kurtzke, 1983). Fatigue was assessed using the Modified Fatigue Impact Scale (MFIS)(Frith and Newton, 2010).

2.3. Evaluation of Sleep Characteristics

Objective sleep characteristics were assessed using the Actisleep (ActiGraph; Pensacola, FL). Actisleep (Peach et al. , 2014) is a tri-axial accelerometer developed to measure sleep/wake positions, sleep latency (SL; time in minutes needed to fall asleep, also called sleep onset), sleep efficiency (SE; number of sleep minutes divided by the total minutes the subject was in bed), total sleep time (TST; total time in minutes between sleep onset and wake), wake after sleep onset (WASO; time of wake in minutes after sleep onset). Better sleep quality is associated with lower SL, lower WASO, higher TST and higher SE. Normal values for each variable are the following: SL<30 minutes, SE ≥85%, TST between 6 to 8 hours and WASO< 30. Actisleep was found to be valid and reliable device for sleep measurements when wore at wrists in healthy young adults (Slater, Botsis, 2015). The clinical utility for using the Actisleep with MS individuals has been proven in several studies (Brass etal. , 2010, Melamud, Golan, 2012, Motl et al. , 2006,Taphoorn et al. , 1993).

Participants were asked to wear the Actisleep for 7 consecutive days during day and nights. They were asked to wear the Actisleep around the non-dominant wrists. Participants were also instructed to behave naturally. Actisleep signals were sampled with 30 Hz. Data from Actisleep was analyzed using Actilife software (ActiGraph;

Pensacola, FL)(Slater, Botsis, 2015). Non-wear periods were excluded from the analysis. Only days with more than 10 hours wear time were included in the analysis. We concluded using 4 days of more than 10 hours wear time for each participant. This method were chosen based on the recommendations of the Actigraph quality control study in which it was advised for the inclusion of at least 4 days of 10 hours wear time in order to assure quality of data (Colley et al. , 2010).

2.4. Evaluation of Physical Activity

Physical activity levels were assessed using mobility accelerometer (Actigraph)(ActiGraph; Pensacola, FL),a valid and reliable tri-axial accelerator to monitor mobility in multiple sclerosis (Motl, McAuley, 2006). Participants were instructed to wear the Actigraph around the waist for 7 days during all waking hours except while swimming or showering. Actigraph signals were sampled with 30 Hz. Activity was calculated for all axes for 10 second periods. Non-wear periods were excluded from the analysis. Only days with more than 10 hours wear time for 4 days were included in the analysis. This method was chosen based on the recommendations of the Actigraph quality control study in which they advised for the inclusion of at least 4 days of 10 hours wear time in order to assure quality of data (Colley et al. , 2010). This data quality control method (i.e. at least 10 hours for 4 days) is essential to reduce the limitations when assessing different levels of physical activity including the low (LA), moderate (MA) and vigorous (VA) levels of physical activity.

Data from Actigraph was downloaded and analyzed using Actilife software (ActiGraph; Pensacola, FL)(Kos et al. , 2007). The unit of the Actigraph is counts per minute (CPM) (ActiGraph; Pensacola, FL). Counts were simply defined as a series of numbers representing the frequency and intensity of movement(Talkowski, 2008).

Physical activity data was processed with Freedson adult algorithm (Freedson et al. , 1998), to obtain total daily and hourly counts per minute (CPM) of light (LA), moderate (MA), vigorous (VA) and moderate to vigorous physical activities (MVPA) (Freedson, Melanson, 1998). According to Freedson adult algorithm, cut-point of these activities were defined as the following: LA: 100 - 1951 CPM, MA: 1952 - 5724 CPM and VA: 5725 - 9498 CPM(Freedson, Melanson, 1998). Minutes per day spent in LA, MA and VA were also extracted.

2.6. Statistical Analysis

Data were visually assessed for normality using histograms and Q-Q plots to allow for the appropriate choice of statistical test. All parameters of sleep characteristics and physical activity levels were normally distributed. Data were checked for the presence of outliers using casewise diagnostic procedure (Field A., 2009); cases where standardized residuals (differences between observed and predicted values divided by an estimate of their standard deviation) were greater than 1.96 or lesser than -1.96 were considered to be outliers (i.e. cases where standardized residuals were outside 2 SD of their distribution). Means and standard deviations of all variables were extracted.

As normality was confirmed for all variables, bi-variate correlational analysis between variables was conducted using Pearson's coefficient with SPSS software (version 19;Chicago, IL). In general, r values <0.10 are considered to be a small effect, >0.10 to <0.50 a moderate effect and >0.50 a large effect (Cohen, 1977). To account for confounding factors including age, body weight, and disease severity as assessed by the EDSS, the correlations between sleep parameters and physical activity parameters were additionally examined using partial correlation analysis.

Bonferroni corrections were used to reduce a possibility of type-I errors resulting from multiple comparisons. For this purpose, the variables were divided into 4 sets of correlations based on the number of variables in the Actisleep measurements (4 variables; SL, SE, TST and WASO). The Bonferroni-corrected significance level (α) was determined by dividing 0.05 by 4 (i.e. the number of variables in the Actisleep measurements). Thus, level of significant was set at 0.0125 (i.e. 0.05/4 = 0.0125).

Results

Demographic data of participants are displayed in Table 1. The mean age was 35.6 ± 9.1 years and range score of EDSS for the participants was 0-5 units. Participants' sleep characteristics and physical activity levels are reported in Table 2.

<Insert Table 1 here>

<Insert Table 2 here>

As in Table 3, subsequent Pearson’s correlation tests showed significant moderate relationships between physical activity and sleep characteristics; WASO correlated significantly with LA and MA ($P<0.0125$). These correlations remained significant even after accounting for age, body weight, fatigue and disease severity (Table 4). In addition, MA and MVPA correlated significantly with fatigue (Table 5).

<Insert Table 3 here>

<Insert Table 4 here>

<Insert Table 5 here>

Discussion

To our knowledge, this is the first study to investigate the relationship between physical activity levels and sleep characteristics in individuals with MS. The results showed that TST is correlated positively with MA and LA. Most importantly, moderate physical activity (i.e. MA and MVPA) was associated with improved sleep quality (i.e. WASO).

Although MA and MVPA have positive correlations with sleep quality measurements, VA didn't show any correlation, whereas LA showed a negative correlation with sleep quality. These findings are similar to previous findings showing that modereate intensity exercise is more tolerated and have more beneficial effects on quality of life and fuctional capacity in MS individuals than vigorus exercises (Dalgas et al. , 2008). Additionally, the current results including MA and MVPA relationships with WASO are consistent with the results from previous studies in other populations, including older adults and Alzheimer disease patients(Eggermont et al. , 2006, Li et al. , 2004). Studies have shown that low and moderate intensity exercises could help improving sleep quality in the older individuals (Li, Fisher, 2004). In agreement of these findings, moderate intensity exercises improved sleep quality and daily life activities in patients with Alzheimer disease and Parkinson's disease (Eggermont, Swaab, 2006, Nascimento, Ayan, 2014).

In data reported here, the average minutes spent in MA was 32 minutes per day. This finding is consistent with the findings from another study in MS (Beckerman et al. , 2010). This suggests that moderate levels of physical activity for at least 30 minutes a day might be important for people with MS to have a better sleep quality. In line with this finding, King el al. have reported that 35-40 minute of moderate exercise for 5 times a week have modest positive effects on sleep quality in older adults who have mild to moderate sleep deficits (King, Pruitt, 2008). This is consistent with the international recommendations for regular physical activity in which people are advised to accumulate at least 30 minutes a day of moderate physical activity during all or most days of the week to obtain health benefits(Organization, 2015).

In order to give recommendations for clinician, researchers, and MS individuals about exercises that might benefit their sleep quality we found it easier to define the moderate exercise in terms of metabolic equivalents (METs). According to the World Health Organization (WHO), moderate activities were defined as physical activities which have METs between 3.0–5.9 (Organization, 2015). Accordingly, data reported here indicates that individuals with MS may benefit their sleep quality by moderate levels of exercise (i.e., physical activity or exercise for 30 minutes a day with of 3-5.9 METs). Therefore, activities such as brisk walking and gardening (Organization, 2015) can be advisable to MS individuals in order to improve their sleep quality.

Overall, the relationships between physical activity and sleep characteristics in the current study are moderate in strength (i.e. r ranged from 0.35 to 0.4). It should be noted however, that these findings are in agreement with other studies that conducted in other populations including children (Orsey et al. , 2013), adolescents (Orsey, Wakefield, 2013) and older adults(Lambiase et al. , 2013). In these studies physical activity were found to moderately correlate with sleep characteristics such as SE and WASO (Lambiase, Gabriel, 2013, Orsey, Wakefield, 2013). These moderate relationships observed in our study between physical activity levels and sleep characteristics in MS individuals suggest that factors other than the decline in physical activity including pain, depression, fatigue and medications may contribute to adverse influence on sleep quality in this population. Future studies examining the combined effect of these factors on sleep quality in MS individuals are warranted.

The positive correlation between LA and WASO indicates that a sedentary life style may cause worse sleep quality in this population. Given that MS individuals usually live sedentary life (Ng and Kent-Braun, 1997), the data reported here suggest that they need to participate in moderate activities in order to have better sleep quality. However, these results need to be confirmed with future longitudinal studies.

The absence of positive correlations between VA and sleep quality can be explained by the potential of the negative influence that fatigue might have on the ability of MS individual to perform VA (Freal et al. , 1984). Thus, MS individuals may not have the ability or may ignore doing vigorous exercise; this is clear from the low mean recorded for VA. This is also supported by the negative correlations which we found between fatigue score and MVPA. Within the context of exercise performance, this observation can be viewed in the light of the dynamic bi-directional relationship of exercise and fatigue. There is growing evidence that exercise affect fatigue in people with MS and vice versa (Motl et al. , 2012). Thus, a vicious cycle might exist in which reduced levels of physical activity is anticipated due to more perceived fatigue that could be experienced in performing higher levels of exercise. Reduced levels of activity may in turn contribute to more rapid decline in fitness and more perceived fatigue overtime. It is therefore imperative to encourage exercise and physical activity from an early stage of the disease in the MS population. Future research needs to focus on important physiological and psychological variables that may serve to mediate the relationship between exercise and fatigue and the possible bi-directional relationship within this context.

Overall, this study suggests that intensity of exercise might be an important consideration on prescribing exercise to improve sleep quality for MS individuals. People with MS should be encouraged to regularly get involved in moderate physical activity as part of treatment plan to improve sleep quality. Thus, moderate exercise could be used as an adds-on therapy to manage sleep problems in MS individuals.

Extending this work to involve a longitudinal design to examine the association of exercise to changes in sleep characteristics in individuals with MS is warranted. In Parkinson's patients, physical activity has been considered as a non-pharmacological strategy to manage sleep (Korczyn, 2006). However, longitudinal, interventional and non-interventional, studies are needed to examine the effect of exercise on sleep in individuals with MS.

This study is not without limitations. For example, the study lacks the gold standards measurements of sleep characteristics (i.e. Polysomnography) which give more clear and understandable picture about sleep characteristics and structure. However, in this study we investigated both physical activity and sleep characteristics objectively. In addition, the participants were restricted to relapsing remitting multiple sclerosis with a young age individuals (mean=35.62 years) and low EDSS score (mean=2.47 unit). Moreover, participants were not screened for co-existing sleep disorders at baseline. Future work with a larger cohort that includes patients across the continuum of the disease severity with different types of MS is needed to confirm our findings. Additionally, extending this work to involve a longitudinal design to examine the association of different exercise intensities with sleep characteristics overtime in people with MS is warranted.

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Table 1: Demographics of study participants (n=60)	
	Mean ± SD, (range)
Age (years)	35.62 ± 9.14
EDSS (units)	2.47 ± 1.63, (0-5)
Years since diagnosis (years)	7.29 ± 4.37
Height (centimeters)	165.77 ± 15.12
Weight (kilograms)	73.56 ± 19.67693
MFIS score	44.08 ± 19.15
EDSS: Kurtzke Expanded Disability Status Scale; MFIS: Modified Fatigue Impact Scale;SD: standard deviation.	

Table 2:Sleep and Physical Activity Characteristics in MS patients (n=60)	
	Mean ± SD
SL (minutes)	23.89 ± 13.23
SE (%)	87.52 ± 76.89
TST (minutes)	353.25 ± 63.98
WASO (minutes)	83.84 ± 42.23
LA (counts)	11660.15 ± 18145.76
MA (counts)	212.04 ± 148.67
VA (counts)	9.70 ± 9.26
MVPA (counts)	222.88 ± 154.60
Minutes/day in LA	557.20± 24.51
Minutes/day in MA	32.02 ±22.53
Minutes/day in VA	10.78± 7.14
LA: light activity; MA: moderate activity;MVPA: total moderate to vigorous physical activity; SD: standard deviation; SE: sleep efficiency; SL: sleep latency; TST: total time in sleep; VA: vigorous activity;;WASO: wake after sleep onset.	

Table 3: Correlations between physical activity and sleep characteristics in MS patients (n=60)					
		LA	**MA**	**VA**	**MVPA**
SL	r	-0.11	0.042	-0.023	0.04
	p-value	0.45	0.77	0.87	0.80
SE	r	0.09	-0.04	-0.13	-0.05
	p-value	0.53	0.79	0.38	0.75
TST	r	0.22	0.35*	0.06	-0.02
	p-value	0.13	0.01	0.69	0.80
WASO	r	0.40**	-0.35**	-0.12	**-0.35***
	p-value	0.004	0.012	0.38	0.014

LA: light activity; MA: moderate activity; MVPA: total moderate to vigorous physical activity; SE: sleep efficiency; SL: sleep latency;TST: total time in sleep; VA: vigorous activity; WASO: wake after sleep onset;** Correlation is significant at the 0.0125 level;

Table 4: Partial correlations between physical activity and sleep characteristics in MS patients (n=60)					
Control variables			**LA**	**MA**	**MVPA**
Age, EDSS,Weight and MFIS	WASO	r	0.39	-0.29	-0.29
		p-value	0.007	.046	0.05

EDSS:Kurtzke Expanded Disability Status Scale; LA: light activity; MA: moderate activity; MVPA: total moderate to vigorous physical activity;; WASO: wake after sleep onset.

Table 5: Correlations between physical activity and fatigue in MS patients (n=60)					
		LA	**MA**	**VA**	**MVPA**
MFIS	r	-0.022	-0.279*	-0.140	-0.28*
	p-value	0.872	0.035	0.301	0.036

LA: light activity; MA: moderate activity; MVPA: total moderate to vigorous physical activity;MFIS: Modified Fatigue Impact Scale; * Correlation is significant at the 0.05 level.

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Highlights

- There are significant correlations between sleep and physical activity in MS.
- This study showed the importance of doing moderate activities in order to have better sleep quality rather than light or vigorous activities in the MS population.
- This study suggest that moderate exercise could be used as an adds-on therapy to manage sleep problems in MS people.