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Investigation of the relationship between fatigue with vitamin D, disease stage, anxiety and physical activity level in patients with Parkinson's disease

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ABSTRACT

Aims: The aim of this study was to investigate the relationship between fatigue severity with vitamin D level, disease stage, anxiety and, physical activity level in patients with Parkinson's disease (PD).

Methods: This study included 66 (male=38, female=28) individuals diagnosed with PD. Fatigue severity was evaluated by the fatique severity scale, vitamin D level by blood test results, anxiety by the Beck Anxiety Inventory (BAI), disease stage by Hoehn-Yahr (HY) staging, and physical activity level by the International Physical Activity Questionnaire (IPAQ-short form).

Results: The study included 66 (male=38, female=28) individuals diagnosed with PD. Fatigue severity was assessed by the fatique severity scale, vitamin D level by blood test results, anxiety by the BAI, disease stage by HY staging, and physical activity level by the IPAQ-short form. In addition, a significant correlation was found between fatigue severity with vitamin D level, anxiety, disease stage, and physical activity level in men, women, and all patients ($p<0.05$).

Conclusion: In Parkinson's patients, fatigue may be related to disease stage, anxiety, physical activity level, and vitamin D level. We suggest that these results should be taken into consideration in fatigue coping strategies for patients with PD.

Keywords: Fatigue, vitamin D, anxiety, physical activity, Parkinson's

INTRODUCTION

Parkinson's disease (PD) is among the most prevalent neurodegenerative conditions, stemming from a combination of environmental and genetic factors, and characterized by gradual progression over time. It comprises motor and sensory symptoms attributed to the degeneration of dopaminergic neurons in the substantia nigra.[1] Its global prevalence stands at approximately 3.28 percent,[2] while in Turkiye, it is around 1.1 percent.[3]

In PD, primary motor symptoms include tremor, rigidity, postural instability, akinesia, and bradykinesia. Secondary symptoms include slowing of activities of daily living, spasticity, mask face, gait disturbances, and kinesiophobia.[4]

Current studies emphasize that sensory symptoms such as depression, cognitive disorders, and fatigue are common in PD in addition to motor symptoms.[5] Since the concept of fatigue in PD was first emphasized by James Parkinson, studies explaining the prevalence, pathophysiology, and impact of fatigue have been carried out in the following periods.[6] The incidence of fatigue was reported to be 33-58% higher in PD patients compared to their healthy counterparts in the study conducted by Freidman et al.[6] Other studies have shown that fatigue is one of the most important barriers to participation in activities of daily living for patients with PD.[7] It has been reported that physical exertion, sleep disorders, inadequate rest, vitamin D levels, and depression levels are associated with physical fatigue in patients with PD.[8,9]

Nowadays, fatigue in patients with PD is an important parameter for research and clinically relevant.[10] The impact of fatigue on the quality of life of people with PD is well known. However, the etiology and pathogenesis of the disease need to be better understood. Many factors (biological, psychosocial, clinical, etc.) may play a role in the development of fatigue in PD.[9,11,12] It is important to elucidate these factors to prevent fatigue. To date, studies have not sufficiently examined the factors associated with fatigue in PD.

This study aimed to investigate the relationships between fatigue severity with vitamin D level, disease stage, anxiety, and physical activity level in patients with PD.

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METHODS

This study involved individuals diagnosed with PD and was approved by the Muş Alparslan University Scientific Researches and Publication Ethics Committee (Date: 07.03.2024, Decision No: 53), conducted in adherence to the Declaration of Helsinki. Prior to the commencement of the study, informed consent, both verbal and written, was obtained from all participants. The study included 66 individuals diagnosed with PD who applied to Kırşehir Ahi Evran University Neurology Outpatient Clinic. Inclusion criteria were as follows: (1) being diagnosed with PD by a specialist neurologist; (2) not having any additional neurologic or orthopedic disorders; (3) having a mini-mental status test score of 24 or above; and (4) voluntarily agreeing to participate in the study. Individuals who were taking medication for depressive symptoms, scored 5 points according to Hoehn-Yahr (HY) staging, could not be contacted, and had conditions that may affect fatigue (such as thyroid dysfunction, anemia, and cardiac problems that may cause physical exertional impairment) were not included in the study.

Evaluation Tools

Demographic information such as age, gender, body mass index, and disease duration was recorded before clinical evaluations. Fatigue level was assessed by the Fatique Severity Scale (FSS), vitamin D level by a blood test, disease stage by HY staging, anxiety level by the Beck Anxiety Inventory (BAI), and physical activity level by the International Physical Activity Questionnaire (IPAQ-short form).

Fatigue severity: In patients with PD, fatigue is a factor that negatively affects the functional status and quality of life of patients. The FSS is a valid and reliable scale for assessing the severity of fatigue in patients with PD, and its use is recommended in the literature.[13,14] In this study, the FSS was used to evaluate severity of fatigue in patients with PD. The FSS assesses fatigue with nine questions. Each question is scored from 0 (strongly disagree) to 7 (agree). The total number of points is obtained by dividing the sum of the points obtained from each of the questions by 9. A high score on the scale indicates an increased severity of fatigue.[13,14]

Vitamin D level: Vitamin D levels of patients with PD were evaluated by HPLC method using Chroms Systems Kit on an Agilent 1200 device. The score obtained from the device was recorded in ng/ml.[15]

Disease stage: HY staging was used to evaluate the stage of PD. According to HY staging, PD are divided into five stages.[16]

Anxiety level: Patients' anxiety levels were assessed using the Turkish version of the BAI.[17] The BAI assesses patients' anxiety levels and consists of 21 questions. Each question is rated from 0 (none) to 3 (severe). The maximum number of points that can be obtained from the scale is 63, and a high number of points indicates the presence of severe anxiety.[18]

Physical activity level: The physical activity level of patients with PD was assessed using the IPAQ-short form. The questionnaire consists of 7 questions assessing the time patients spent physically in the last 1 week. The criterion for physical activity was at least 10 minutes at a time. The duration of vigorous and moderate physical activity, walking, and sitting time were recorded. Sitting time was calculated separately as sedentary behavior. The "MET-minutes/day" score was obtained by multiplying minutes, days, and metabolic equivalent task (MET) values. A total physical activity score was obtained by multiplying 3.3 METs by walking time, 4 METs by moderate physical activity, and 8 METs by vigorous physical activity. A total score below 600 MET-min/week was defined as low level physical activity, 600-3000 MET-min/week as moderate level, and above 3000 MET-min/week as high level physical activity.[19]

Statistical Analysis

SPSS (Version 25.0. Armonk, NY, IBM Corp.) software was used to perform statistical analyses. In statistical analysis process, the results are represented as mean±standard deviation for continuous variables. For nominal variables, numbers and % were used. In order to carry out the signifance tests between genders, the independent samples t-test is applied with α=0.05 level. Factors associated with fatigue severity were evaluated by Pearson correlation analysis in parametric conditions. The correlation degree was interpreted as follows: low correlation from 0.05 to 0.4, moderate correlation from 0.4 to 0.7, and high correlation from 0.7 to 1.0, based on the correlation coefficients.[20]

RESULTS

The demographic data and the clinical evaluation of the patients with PD are shown in Table 1. Mean age of patients enrolled in this study was 69.48±9.74 years.

Table 1. Demographic characteristics of the participants

Variables	Mean±SD	Minimum	Maximum
Age (years)	69.48±6.74	41.00	87.00
BMI (kg/m^2)	25.57±1.70	21.56	30.03
Duration of disease (years)	4.61±2.73	1.00	10.00
Vitamin D level (ng/ml)	21.65±4.20	4.00	56.00
FSS	4.23±1.43	1.80	7.00
HY staging	2.58±0.84	1.00	4.00
BAI	29.39±6.41	10.00	52.00
IPAQ-short form (metabolic equivalent task)	624.06±76.66	400.00	850.00

SD: Standart deviation, BMI: Body mass index, HY: Hoehn-Yahr, IPAQ: International physical activity questionnaire, FSS: Fatique severity scale, BAI: Beck anxiety inventory

The comparison of the variables of Parkinson's patients included in the study according to gender is given in Table 2. According to this table, no statistically significant difference was found for any variable when comparing all variables of patients by gender (p>0.05).

The relationship between fatigue severity and other variables in females, males, and all patients included in the study is given in Table 3. When the relationship between the severity of fatigue in male Parkinson's patients and other variables

was examined, it was found that there was a negative, high-level statistical relationship between the severity of fatigue and vitamin D and physical activity levels of male patients, while there was a positive, high-level statistical relationship between disease stage and anxiety severity ($p<0.05$) (Table 3).

Table 2. Comparison of variables of patients with PD according to gender

Variables	Male (n=38) Mean±SD	Female (n=28) Mean±SD	t	p
Age (years)	71.42±8.62	68.86±7.68	1.921	0.059
BMI (kg/m²)	25.64±1.90	25.47±1.43	0.384	0.703
Duration of disease (years)	4.32±3.24	5.00±4.35	-0.733	0.466
Vitamin D level (ng/ml)	19.66±3.06	24.36±5.25	-1.710	0.092
FSS	4.44±1.39	3.95±1.48	1.369	0.176

PD: Parkinson's disease, SD: Standard deviation, BMI: Body mass index, FSS: Fatique severity scale, t: Independent samples t-test

Table 3. Examination of the relationship between fatigue severity and other variables in female, male and all patients included in the study

Variables		Male (n=38) FSS	Female (n=28) FSS	All patients (n=66) FSS
Age (years)	r	-0.014	-0.021	0.023
	p	0.934	0.916	0.856
BMI (kg/m²)	r	-0.153	0.118	-0.043
	p	0.360	0.551	0.730
Duration of disease (years)	r	0.134	-0.075	0.011
	p	0.424	0.705	0.929
Vitamin D level (ng/ml)	r	-0.791	-0.908	-0.851
	p	<0.001*	<0.001*	<0.001*
HY staging	r	0.897	0.854	0.879
	p	<0.001*	<0.001*	<0.001*
BAI	r	0.845	0.723	0.797
	p	<0.001*	<0.001*	<0.001*
IPAQ-short form (metabolic equivalent task)	r	-0.808	-0.695	-0.757
	p	<0.001*	<0.001*	<0.001*

FSS: Fatique severity scale, BMI: Body mass index, HY: Hoehn-Yahr, BAI: Beck anxiety inventory, IPAQ: International physical activity questionnaire, r: Pearson correlation coefficient, *p<0.001

Similarly, when the relationships between the severity of fatigue and other variables in female Parkinson's patients included in the study were examined, it was found that there was a negative, high-level statistical correlation between the severity of fatigue and vitamin D and physical activity levels of female patients, while there was a positive, high-level statistical relationship between disease stage and anxiety severity ($p<0.05$).

When the relationships between fatigue severity and other variables in all PD patients were examined, it was found that there was a negative, high-level statistical relationship between fatigue severity and vitamin D and physical activity levels, while there was a positive, high-level statistical relationship between disease stage and anxiety severity ($p<0.05$)(Table 3).

DISCUSSION

This study investigated relationships between the severity of fatigue with age, BMI, disease duration, vitamin D level, disease stage, anxiety level, and physical activity level in patients with PD. Significant relationships were found between fatigue severity and vitamin D level, disease stage, anxiety level, and physical activity level in patients with PD. Additionally, when compared in terms of gender in Parkinson's patients, there was no difference in these parameters between male and female participants.

In a review of the literature, Koçer et al.[21] examined the motor and non-motor symptoms related to fatigue in patients with PD and divided Parkinson's patients into three groups: fatigued, non-fatigued, and all Parkinson's patients. They found that there were no significant differences between the groups regarding gender, disease duration, or age also concluded that male Parkinson's patients had less fatigue compared to female Parkinson's patients, but this trend was not significant.[21] In another study, Herlofson and Larsen[22] and Martinez Martin et al.[23] reported that age and disease duration were not significantly related to fatigue severity. In this study, we concluded that there was no significant relationship between severity of fatigue with duration of disease, age and that there was no significant difference in the severity of fatigue between male and female PD patients.

Decreased vitamin D levels are frequently observed in patients with PD. It has been observed that the vitamin D levels of Parkinson's patients are considerably reduced compared to healthy individuals.[24] Zhang et al.,[8] when they compared Parkinson's patients and healthy individuals, stated that vitamin D levels were lower in Parkinson's patients, but they said that vitamin D levels were not related to fatigue severity in Parkinson's patients. Sleeman et al.[25] found that low vitamin D levels were associated with disease severity in Parkinson's patients. Moghaddasi et al.[26] concluded that low vitamin D levels in Parkinson's patients were associated with the severity of motor effects such as postural instability, postural anomalies, and freezing gait. In this study, a negative relation was found between severity of fatigue and vitamin D level which may be attributed to the fact that a low vitamin D level in Parkinson's patients causes abnormal motor movements and consequently more energy consumption in participation in activities of daily living.

In PD, fatigue is one of the most prevalent non-motor symptoms that can be present in the early stages of the disease, often persisting after initial onset, and gradually worsening over time.[27] As a consequence, fatigue can limit Parkinson's patients' participation in activities of daily living as well as negatively affect their quality of life.[27] There is no clear understanding of the pathological conditions that cause PD or the mechanisms by which they cause fatigue. Herlofson and Larsen[22] reported that fatigue in PD is associated with disease stage. Elbers et al.[28] evaluated the disease stage using HY staging in a study conducted in idiopathic Parkinson's patients. They found a significant relationship between disease stage and fatigue severity in idiopathic Parkinson's patients.[28] Other studies have also shown a relationship between disease stage and fatigue severity.[10,29] This study results are consistent with the literature. In this study, a significant relation was observed between fatigue severity and disease stage in men, women, and all Parkinson's patients. We may attribute this result to the worsening of motor symptoms in parallel with the increase in disease stage, which increases the severity of fatigue.

Studies have shown that psychological treatment of both motor and non-motor symptoms in people with

PD is effective in improving both cognitive and physical symptoms.[30] There are studies showing that fatigue in PD is associated with psychological factors such as anxiety, sleep disorders, depression, and apathy.[31] Siciliano et al.[32] stated that psychological factors may be related to fatigue in patients with PD. Gołąb-Janowska et al.[33] reported that depression was associated with fatigue severity in idiopathic Parkinson's patients. In another study, Havlikova et al.[10] evaluated the severity of fatigue in Parkinson's patients with a multidimensional fatigue inventory. When the study findings were analyzed, it was concluded that fatigue severity was related to anxiety and depression levels.[10] In the present study, a significant relationship was found between fatigue and anxiety severity in Parkinson's patients. This result may have occurred due to the abnormal activity and connections of limbic-cortical circuits and the degeneration of serotoninergic pathways.[34,35]

In the literature, studies examining fatigue severity and physical activity levels in patients with PD have shown different results. Increased physical activity in patients with PD has been shown to increase physiological stress. This has been related to increased fatigue severity.[36] Gaerber and Friedman[37] concluded that the increase in the severity of fatigue in patients with PD was related to a low level of physical activity. Increased fatigue severity in idiopathic PD patients was reported to be associated with lower physical activity levels.[28] Lana et al.[38] stated that fatigue severity was not a predictive factor of physical activity level. In the current study, a significant negative relationship was found between fatigue severity and physical activity level in Parkinson's patients. Despite these results, it is still controversial whether fatigue is the cause or consequence of decreased physical activity levels.

Limitations

This study has several limitations. The first is that there was no control group in our study to compare the clinical, biological, and psychological evaluations of Parkinson's patients with their healthy peers. Another limitation is that we did not question the type of PD in patients. In future studies, it may be useful to examine the factors associated with fatigue in PD according to different PD types.

CONCLUSION

In the present study, which investigated the factors associated with fatigue in patients with PD, vitamin D level, disease stage, anxiety, and physical activity level were found to be associated with fatigue severity. We suggest that factors associated with fatigue severity should be taken into consideration when designing treatment programs and evaluating the effectiveness of interventions in patients with PD.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Muş Alparslan University Scientific Researches and Publication Ethics Committee (Date: 07.03.2024, Decision No: 53).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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