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INVESTIGATION OF THE RELATIONSHIP BETWEEN FATIGUE, DEPRESSION AND NUTRITIONAL STATUS IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS

Ataklarla Seyreden Multipl Skleroz Hastalarında Yorgunluk, Depresyon Ve Beslenme Durumu Arasındaki İlişkinin İncelenmesi

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ABSTRACT

This study aimed to evaluate the nutritional status, depression and fatigue status of patients with Relapsing Remitting Multiple Sclerosis (RRMS). The study was carried out on 30 MS patients (Patient Group: PG) and a control group consisting of 30 healthy volunteers with similar characteristics (Control Group: CG). It was found that the relationship between depression and fatigue among MS patients was positive ($p<0.05$). The mean score of the Fatigue Severity Scale (FSS) was 5.65±1.57 in PG patients and 3.10±0.97 in CG patients. The fatigue level of the patients was significantly higher than that of the controls ($p<0.05$). A negative correlation was found between vitamin B12 intake and the scores of the FSS and Beck Depression Inventory (BDI) in patients with PG ($p<0.05$). The study showed that fatigue and depression in MS patients were closely related their dietary habits. Since low serum B12 levels may increase the risk of fatigue and depression, attention should be paid to vitamin B12 intake. In order to improve the quality of life of MS patients, their nutrition should be closely monitored and a balanced and healthy nutrition plan appropriate to their needs should be implemented.

Keywords: Depression, Fatigue, Multiple sclerosis, Nutrition.

ÖZ

Bu çalışma ataklarla seyreden Multipl Skleroz (MS) hastalarının beslenme, depresyon ve yorgunluk durumlarını değerlendirmeyi amaçlamıştır. Çalışma, 30 MS hastası (Hasta Grubu: HG) ve benzer özelliklerdeki 30 sağlıklı gönüllüden oluşan kontrol grubu (Kontrol Grubu: KG) üzerinde gerçekleştirilmiştir. MS'liler arasında depresyon ve yorgunluk arasındaki ilişkinin pozitif yönlü olduğu bulunmuştur ($p<0.05$). HG'dekilerin Yorgunluk Şiddeti Ölçeği (YŞÖ) ortalama puanı 5.65±1.57 iken, KG'dekilerin 3.10±0.97'dir. Hastaların yorgunluk düzeyi kontrollere göre anlamlıdır ($p<0.05$). HG'dekilerin B12 vitamini alımı ile YŞÖ ve Beck Depresyon Ölçeği (BDÖ) puanları açısından negatif yönlü ilişki bulunmuştur ($p<0.05$). Çalışma MS hastalarının yorgunluk ve depresyon durumlarının beslenme alışkanlıkları ile yakından ilişkili olduğunu göstermiştir. Düşük serum B12 seviyeleri yorgunluk ve depresyon riskini artırabileceğinden B12 vitamini alımına dikkat edilmelidir. MS hastalarının yaşam kalitesini artırmak için beslenmeleri yakından takip edilmeli, ihtiyaçlarına uygun, dengeli ve sağlıklı bir beslenme planı uygulanmalıdır.

Anahtar kelimeler: Beslenme, Depresyon, Multipl skleroz, Yorgunluk.

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INTRODUCTION

Multiple sclerosis (MS), originating from genetic and environmental factors affecting the Central Nervous System (CNS), is the most common chronic inflammatory disease that causes irreversible neurological damage and symptoms, involving young adults between the ages of 20-40 (Kobelt, Thompson, Berg, Gannedahl & Eriksson, 2017). The prevalence and incidence of MS are increasing in developed and developing countries and the underlying cause is unclear (Browne et al., 2014). MS is more common in females and this ratio is close to 3:1 (F:M) in developed countries (Orton et al., 2006). Relapsing Remitting Multiple Sclerosis (RRMS) is the most common type among all other MS types constituting 85% (Manousaki et al., 2017). MS affects the quality of life of individuals negatively by causing motor, cognitive, sensory, mental, intestinal, bladder, sexual function, visual function and sleep disorders as a result of the demyelination of neurons (Dendrou, Fugger & Friese, 2015). Fatigue, muscle coordination disorders and motor impairments are common in many patients. The disease manifests itself in sensory symptoms (Compston, Winedl & Kieseier, 2008). Around 70-80% of patients experience fatigue as it significantly affects the level of physical activity (Türk Nöroloji Derneği, [TND], 2020). It is thought that there is an essential relationship between bowel dysfunction and fatigue. Increased fatigue may lead to a decrease in the ability to exercise and thus aggravate constipation symptoms (Wollin, Bennie, Leech, Windsor & Spencer, 2005). Depression is observed in 50% of the patients. The suicide rate due to depression is high in MS patients. In addition, anxiety and bipolar disorders can also develop (Garg & Smith, 2015). It is thought that depression among MS patients may decrease their motivation and cause them to stay away from social life by negatively affecting their quality of life. At the same time, sleep disorders, anxiety, fatigue and eating disorders may accompany depression (Feinstein, Magalhales, Richard, Audet & Moore, 2014). Since MS is an autoimmune disease, a multidisciplinary treatment approach is required. The treatments' aim is to reduce neurological damage and the frequency of the recurrence of attacks, to prevent disability as a result of attacks, and to alleviate symptoms. The aim of this study is to evaluate the relationship between depression, fatigue and nutritional status in individuals diagnosed with RRMS.

MATERIAL AND METHOD

Desing

This is a case-control study.

Setting and Participants

The study included 30 patients aged 19-64 years who were admitted to the neurology outpatient clinic of the medical faculty of Erciyes University Hospital in Kayseri and diagnosed with RRMS according to the 2017 revisions of the McDonald criteria (Thompson et al., 2018). This study was carried out on a total of 60 people, including 30 healthy volunteers with similar characteristics to the patient group. The exclusion criteria were being younger than 19 years old or older than 64 years old, having cancer or psychiatric diseases, being pregnant and breastfeeding, being in an attack period or being in other MS types other than RRMS.

Data Collection Tools

The data were collected by using the questionnaire form, the food records 24-hour recalls form, anthropometric measurements, Fatigue Severity Scale (FSS) and Beck Depression Inventory (BDI).

Questionnaire Form

Each participant answered a questionnaire form consisting of 19 personal information questions prepared by the researcher. All responses were recorded during face-to-face interviews with the participants.

Food Intake

In order to evaluate the daily energy and nutrient intake of individuals, food consumption was recorded with a food records 24-hour recalls method. Energy and nutrients consumed for a day were calculated using the "BeBis" (Computer Supported Nutrition Program, Nutrition Information System) program (Erdhardt, 2010).

Anthropometric Measurements

The researcher made weight (kg), body height (cm), hip waist circumference (cm) and circumference (cm) measurements of all the individuals participating in the study. The Body Mass Index (BMI) of the individuals was calculated using the equation [body weight (kg)/(height (m))^2] (World Health Organization [WHO], 2011).

Fatigue Severity Scale (FSS)

A scale consisting of 9 items was used to evaluate the fatigue level of individuals. The total score is calculated by averaging the 9 items and the score range of the scale is 1-7. The participant was asked to rate the situation presented in each item from 1 to 7 as 1=Strongly disagree 2=I do not agree 3=I tend not to agree 4=I am indecisive 5=I tend to agree 6=I agree 7=I strongly agree. Cronbach's alpha reliability coefficient of the scale was 0.96 (Armutlu et al., 2007; Krupp, LaRocca, Muir-Nash & Steinberg, 1989).

Beck Depression Inventory (BDI)

It was used to evaluate the depression status of individuals. There are 21 categories in the scale. Each of these categories consists of 4 different evaluation items and is scored between 0 and 3 points. In total, the lowest 0, the highest 63 points are taken. The cut-off value of the scale is 17. Scoring above 17 indicates the presence of depression. Total score; between 0-9 is interpreted as "no depression", 10-16 as "mild depression", 17-29 as "moderate depression", 30-63 as "severe depression". The Cronbach's alpha reliability coefficient of the scale was 0.854 (Beck, Ward, Mendelson, Mock & Erbaugh, 1961; Hisli, 1989).

Ethical Approval

All subjects gave written informed consent in accordance with the Declaration of Helsinki and approval was obtained by the Ethics Committee of Ankara Yıldırım Beyazıt University (Project No: 2019-358).

Statistical Analysis

The data obtained in the study was evaluated through SPSS (Statistical Package for the Social Sciences) 24 package program. Normally distributed continuous quantitative variables are given with mean, standard deviation ($\bar{X}$ ±SD), lower and upper values. Non-normally distributed data are shown with a median and quarterly difference (IQR). Quantitative variables are summarized by number (n) and percentage (%). In all analyzes, $p<0.05$ was accepted as a statistically significant difference.

RESULT

The mean age of the subjects in PG was 38.73±9.9 years, while the mean age of the subjects in CG was 38.20±9.7 years ($p>0.05$). In both groups, 66.7% of the participants were female and 33.3% were male. 43.3% of the subjects in PG and 50% of the subjects in CG were high school graduates ($p>0.05$). The mean age at the diagnosis of MS was 29.7±10.5 years (Table 1).

Table 1. Distribution of General Characteristics of the Participants (%)

General Features	PG (n:30)		CG (n:30)		Total (n:60)		p
	n	%	n	%	n	%	
Age (years) ($\bar{X}$ ±SD)	38.73±9.9		38.20±9.7				0.834*
MS diagnosis(years) ($\bar{X}$ ±SD)	29.7±10.5						
Age(years)							
19-29	4	13.3	6	20.0	10	16.7	
30-39	12	40.0	8	26.7	20	33.3	0.715**
40-49	10	33.4	11	36.7	21	35.0	
50-59	4	13.3	5	16.6	9	15.0	

Gender							
Female	20	66.7	20	66.7	40	66.7	1.000**
Male	10	33.3	10	33.3	20	33.3	
Educational Status							
Primary school	5	16.7	4	13.3	9	15.0	
Secondary school	4	13.3	2	6.7	6	10.0	0.806**
High school	13	43.3	15	50.0	28	46.7	
University	8	26.7	9	30.0	17	28.3	
Marital status							
Married	24	80.0	23	76.7	47	78.3	1.754**
Single	6	20.0	7	23.3	13	21.7	

*Independent Sample t-test, **Pearson-χ^2 test

The mean BMI of females in PG and CG was 27.4±5.2 kg/m^2 and 25.9±5.1 kg/m^2 respectively (p>0.05). The average BMI of males in PG was 25.6±5.1 kg/m^2, and 29.5±4.5 kg/m^2 (p>0.05) for controls. The mean waist/hip ratio of females respectively in PG and CG was 0.82±0.06, 0.77±0.07, and for males 0.93±0.1, 1.01±0.1. The average waist/hip ratio of females in PG and CG proved a statistically significant difference (p<0.05) (Table 2).

Table 2. Individuals' Anthropometric Measurement Means, Standard Deviations (X̄±SD), min-max Values

Anthropometric Measurements	**PG (n:30)**		**CG (n:30)**		
	(X̄ ±SD)	**Median (Min-Max)**	**(X̄ ±SD)**	**Median (Min-Max)**	**p**
Body weight (kg)					
Female	70.6±13.4	70.0 (50.0-103.0)	67.2±11.1	66.5 (50.0-86.0)	0.389*
Male	76.3±17.4	72.5 (50.0-98.0)	90.9±12.3	94.0 (71.0-105.0)	**0.044***
Height (cm)					
Female	160.6±5.6	160.5 (150.0-170.0)	161.6±4.0	161.0 (155.0-170.0)	0.544*
Male	172.2±5.8	173.5 (163.0-182.0)	175.8±3.9	175.5 (172.0-185.0)	0.124*
BMI (kg/m²)					
Female	27.4±5.2	27.6 (19.3-37.8)	25.9±5.1	25.2 (18.6-33.7)	0.364*
Male	25.6±5.1	24.5 (17.9-32.6)	29.5±4.5	31.4 (21.9-35.5)	0.082**
Waist circumference (cm)					
Female	86.4±12.8	86.0 (65.0-120.0)	78.6±12.3	75.0 (63.0-101.0)	0.056*
Male	89.1±17.3	85.0 (67.0-110.0)	99.6±11.6	104.0 (80.0-113.0)	0.129*
Hip circumference					

(cm)					
Female	105.2±11.5	104.5 (89.0-134.0)	101.4±10.2	101.5 (85.0-124.0)	0.303**
Male	95.3±5.7	95.0 (85.0-103.0)	98.6±3.2	98.0 (92.0-103.0)	0.132*
Waist/hip ratio					
Female	0.82±0.0	0.8 (0.7-0.9)	0.77±0.0	0.7 (0.7-0.9)	**0.021***
Male	0.93±0.1	0.9 (0.8-1.1)	1.01±0.1	1.0 (0.9-1.2)	0.139*

* Independent Sample t-test, **Mann-Whitney U test

It was determined that the total BDI mean score of the individuals in PG was 11.4±6.8, while those in CG were 2.5±1.9 ($p<0.05$). While 20% of the individuals in PG had mild depression, 23.3% had moderate and none of the participants in CG had depression ($p<0.05$). In total, 43.3% of individuals in PG have depression. The average score of fatigue severity in PG was 5.65±1.57, while those in CG had a score of 3.10±0.97. Fatigue score was found higher in PG. Fatigue scores between the groups were statistically significant ($p<0.05$) (Table 3).

Table 3. The Distribution of the Depression and Fatigue Status of the Individuals

	Patient Group (n:30)		**Control Group (30)**		**Total (60)**		**p**
	n	**%**	**n**	**%**	**n**	**%**	
BDI Classification							
Depression no (0-9)	17	56.7	30	100.0	47	78.3	
Mild (10-16)	6	20.0	-	-	6	10.0	**p=0.000***
Moderate (17-29)	7	23.3	-	-	7	11.7	
BDI Score ($\bar{X}$ ±SS)	11.4±6.8		2.5±1.9		6.9±6.7		**0.000** **
(Min-Max)	(3.0-29.0)		(0.0-7.0)		(0.0-29.0)		
FSS Score ($\bar{X}$ ±SS)	5.65±1.57		3.10±0.97		4.37±1.82		Z=-5.086
(Min-Max)	(1.44-7.0)		(1.0-5.11)		(1.0-7.0)		**p=0.000*** **

* χ^2- cross tables, **Pearson-χ^2 test,***Mann-Whitney U" test, FSS: Fatigue Severity Scale, BDI: Beck Depression Inventory

There is a moderately significant positive correlation between fatigue score and BDI score of individuals with PG ($r=0.670$; $p=0.000$). A weakly significant positive correlation was found between the BDI score and the fatigue score of individuals in CG ($r=0.447$; $p=0.013$) (Table 4).

Table 4. Evaluation of Individuals' BDI Scores and Their Fatigue Status

		PG(n:30)	**CG(n:30)**
		Fatigue Status	Fatigue Status
BDI Score	*r*	**0.670**	**0.447***
	p	**0.000**	**0.013***

*"Pearson" & "Spearman" correlation coefficient, BDI: Beck Depression Inventory

There is a correlation between BDI scores and anthropometric measurements and energy and nutrient intakes of individuals with PG. A negative, weak and statistically significant

correlation was found between the BDI score and protein (%), fiber, potassium, magnesium, vitamin B1, B6 and B12 values ($p<0.05$) (Table 5).

Table 5. Correlation of BDI Scores with Anthropometric Measurements, Energy and Nutrients in the Patient Group

	BDI Score Patient Group (n:30)	
	r	**p***
Anthropometric Measurements		
Body weight (kg)	0.102	0.590
BMI (kg/m^2)	0.219	0.245
Waist circumference (cm)	0.245	0.191
Dietary Energy/Nutrients		
Energy (kcal/day)	-0.120	0.527
Carbohydrate (%)	0.200	0.290
Protein (%)	**-0.390**	**0.033**
Fat (%)	-0.095	0.619
Cholesterol (mg)	-0.290	0.121
Fiber (g)	**-0.395**	**0.031**
Iron (mg)	-0.312	0.094
Zinc (mg)	-0.300	0.107
Sodium (mg)	-0.037	0.845
Potassium (mg)	**-0.474**	**0.008**
Phosphorus (mg)	-0.341	0.065
Calcium (mg)	-0.334	0.071
Magnesium (mg)	**-0.371**	**0.044**
Vitamin B1 (mg)	**-0.409**	**0.025**
Vitamin B6 (mg)	**-0.361**	**0.049**
Vitamin B12 (mcg)	**-0.443**	**0.014**
Vitamin D (µg)	-0.219	0.244
Vitamin C (mg)	-0.270	0.148

BMI: Body Mass Index, *"Pearson" & "Spearman" correlation coefficient

DISCUSSION

MS affects many regions of the body (Klineova & Lublin, 2018). Most patients display fatigue, muscle coordination disorders and motor disorders (Manjaly et al., 2019). In this study

considering the gender distribution in both groups, women make up twice as much as men. In a study conducted by Ozakbas et al. (2018), 68.6% of 487 individuals with RRMS were women (Ozakbas et al., 2018). In this study, the mean age at MS diagnosis was 29.7±10.5 years. Similarly, in a study conducted by Confavreux and Vukusic (2006) on 844 MS patients, the mean age at diagnosis was 29.5 years (Confavreux, & Vukusic, 2006). In the Nurse's Health study, 121 700 women and in the Nurse's Health II study, 116 671 women were included and it was determined that those with a BMI of 30 kg/m^2 or more at the age of 18 had a 2-fold increased risk of MS in the future (Munger, Chitnis & Ascherio, 2009). In a case-control study including 1571 individuals with MS and 3371 healthy individuals, it was found that the risk of MS increased 2-fold in individuals who exceeded 27 kg/m^2 BMI at the age of 20 years (Hedström, Olsson & Alfredsson, 2012). In a case-control study, BMI of 470 MS and 519 healthy individuals were examined, and it was observed that 37% of MS patients and 32% of healthy individuals were in the obese class (Kankaya, Dogru, Yildirim & Fadiloglu, 2016). In another study, 25.8% of 123 MS individuals were found to be obese (Golden & Voskuhl, 2017). In this study, BMI value for 26.7% of the individuals in PG and 43.3% of the individuals in controls were found to be 30 kg/m^2 and above. Individuals' BMI values were similar to other studies. The difference of this study is that the rate of obese is higher. As an important cofactor in myelin formation, vitamin B12 deficiency has been implicated in axonal degeneration and demyelination. In a study in which 767 individuals with MS and 762 healthy individuals were examined, serum vitamin B12 levels were found to be lower in individuals with MS compared to healthy individuals (Najafi, Shaygannajad, Mirpourian & Gholamrezaei, 2012). This study a negative, weak and statistically significant correlation was found between the BDI score and protein (%), fiber, potassium, magnesium, vitamin B1, B6 and B12 values. In a study, the BDI and FSS were applied to 100 individuals with MS and it was observed that 54% of the individuals were tired and 52% had symptoms of depression. In addition, depression symptoms were observed in 72.2% of the patients who display fatigue (Mirza, 2002). In another study examining 1374 individuals with MS, the presence of depression was observed in 41.8% of the individuals (Oksenberg, Baranzini, Sawcer & Hauser, 2008). In a case-control study, according to the BDI scores of 54 MS patients and 43 healthy individuals, depression was observed in 29 (53.7%) of MS patients and 4 (9.3%) of healthy individuals (Onat, Delialioglu, & Ozel, 2015). In this study gave similar results to other studies. More than half of the individuals PG had depression and the mean FSS score of the individuals was 5.65±1.57. A positive, moderately significant correlation was found between the BDI score and the FSS score of the individuals in PG ($p<0.05$). Fatigue may prove to be associated with depression as it can negatively affect

the quality of life of people and cause the development of depression.

Limitation

One of the limitations of this study is that it was conducted in a single center. The number of people volunteering to participate in the research is limited.

CONCLUSION

Multiple Sclerosis (MS) affects the lives of individuals in many ways. Adverse effects that occur in individuals' physical functions are also reflected in their diet and the disease brings along nutritional problems such as obesity. As a result of depression accompanied by fatigue, it becomes difficult to provide a balanced diet due to imbalanced nutrition and the patients are adversely affected by this situation. People with MS need to maintain adequate and balanced nutrition. Since the disease is characterized by multiple organ involvement, a multidisciplinary approach should be applied in treatment. The dietitians can prevent obesity, malnutrition, vitamin and mineral deficiencies by creating a nutritional plan appropriate for individuals. The purpose should be to increase the quality of life by assisting individuals in maintaining healthy eating habits. More studies are needed to examine the relationship between both nutritional status and fatigue, and emotional appetite and depression in patients with MS.

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REFERENCES

Armutlu, K., Korkmaz, N. C., Keser, I., Sumbuloglu, V., Akbiyik, D. I., Guney, Z., & Karabudak, R. (2007). The validity and reliability of the Fatigue Severity Scale in Turkish multiple sclerosis patients. *International Journal of Rehabilitation Research*, 30(1), 81-85. doi: 10.1097/MRR.0b013e3280146ec4

Beck, A. T., Ward, C., Mendelson, M., Mock, J., & Erbaugh, J. J. A. G. P. (1961). Beck depression inventory (BDI). *Arch Gen Psychiatry*, 4(6), 561-571. doi: 10.1001/archpsyc.1961.01710120031004.

Browne, P., Chandraratna, D., Angood, C., Tremlett, H., Baker, C., Taylor, B. V., & Thompson, A. J. (2014). Atlas of multiple sclerosis 2013: a growing global problem with widespread inequity. *Neurology*, 83(11), 1022-1024. doi:10.1212/WNL.0000000000000768

Compston, A., Winedl, H., & Kieseier, B. C. (2008). Coles. Multiple sclerosis. *Lancet*, 372, 1502-1517.

Confavreux, C., & Vukusic, S. (2006). Natural history of multiple sclerosis: a unifying concept. *Brain*, 129(3), 606-616. doi:10.1093/brain/awl007

Dendrou, C. A., Fugger, L., & Friese, M. A. (2015). Immunopathology of multiple sclerosis. *Nature Reviews Immunology*, 15(9), 545-558. doi:10.1038/nri3871

Erdhardt DJ. Beslenme Bilgi Sistemi (BeBİS) 7.1. 2010.

Feinstein, A., Magalhaes, S., Richard, J. F., Audet, B., & Moore, C. (2014). The link between multiple sclerosis and depression. *Nature Reviews Neurology*, 10(9), 507-517. doi:10.1038/nrneurol.2014.139

Garg N, & Smith TW. An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. *Brain Behav* 2015; 5(9): e00362. doi: 10.1002/brb3.362. doi:10.1002/brb3.362

Golden, L. C., & Voskuhl, R. (2017). The importance of studying sex differences in disease: The example of multiple sclerosis. *Journal of Neuroscience Research*, 95(1-2), 633-643. doi:10.1002/jnr.23955

Hedström, A. K., Olsson, T., & Alfredsson, L. (2012). High body mass index before age 20 is associated with increased risk for multiple sclerosis in both men and women. *Multiple Sclerosis Journal,* 18(9), 1334-1336. https://doi.org/10.1177/1352458512436596

Hisli, N. (1989). Beck Depresyon Envanterinin üniversite öğrencileri için geçerliği, güvenirliği. *Psikoloji Dergisi,* 7(23), 3-13.

Kankaya, H., Dogru, B. V., Yildirim, Y., & Fadiloglu, Ç. (2016). Multipl Skleroz'lu hastaların günlük yaşam aktivite düzeyleri ile bakım verenlerin gösterdiği tepkiler arasındaki ilişkinin incelenmesi. *Gümüşhane Üniversitesi Sağlık Bilimleri Dergisi,* 5(1), 33-49.

Klineova, S., & Lublin, F. D. (2018). Clinical course of multiple sclerosis. *Cold Spring Harbor perspectives in medicine*, 8(9), a028928. doi:10.1101/cshperspect.a028928

Kobelt G, Thompson A, Berg J, Gannedahl M, Eriksson J. New insights into the burden and costs of multiple sclerosis in Europe. *Mult Scler* 2017; 23(8): 1123-1136. doi: 10.1177/1352458517694432

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology,* 46(10), 1121-1123. doi: 10.1001/archneur.1989.00520460115022

Manjaly, Z. M., Harrison, N. A., Critchley, H. D., Do, C. T., Stefanics, G., Wenderoth, N., & Stephan, K. E. (2019). Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*, 90(6), 642-651. doi:10.1136/jnnp-2018-320050

Manousaki, D., Dudding, T., Haworth, S., Hsu, Y. H., Liu, C. T., Medina-Gómez, C. & Richards, J. B. (2017). Low-frequency synonymous coding variation in CYP2R1 has large effects on vitamin D levels and risk of multiple sclerosis. *The American Journal of Human Genetics,* 101(2), 227-238. doi: 10.1016/j.ajhg.2017.06.014. Epub 2017 Jul 27

Mirza, M. (2002). The etiology and the epidemiology of multiple sclerosis. *Erciyes Medical Journal*, 24(1): 40-47.

Munger, K. L., Chitnis, T., & Ascherio, A. (2009). Body size and risk of MS in two cohorts of US women. *Neurology*, 73(19), 1543-1550. doi:10.1212/wnl.0b013e3181c0d6e0

Najafi, M. R., Shaygannajad, V., Mirpourian, M., & Gholamrezaei, A. (2012). Vitamin B12 deficiency and multiple sclerosis; is there any association?. *International Journal of Preventive Medicine*, 3(4), 286.

Oksenberg, J. R., Baranzini, S. E., Sawcer, S., & Hauser, S. L. (2008). The genetics of multiple sclerosis: SNPs to pathways to pathogenesis. *Nature Reviews Genetics,* 9(7), 516-526. doi:10.1038/nrg2395

Onat, Ş. Ş., Delialioğlu, S. Ü., & Ozel, S. (2015). Multipl Sklerozda Depresyon, Fonksiyonel Durum ve Yaşam Kalitesi İlişkisi: Bir Rehabilitasyon Merkezi Deneyimi. *Journal of Physical Medicine & Rehabilitation Sciences,* 18(3).

Orton, S. M., Herrera, B. M., Yee, I. M., Valdar, W., Ramagopalan, S. V., Sadovnick, A. D., & Ebers, G. C. (2006). Sex ratio of multiple sclerosis in Canada: a longitudinal study. *The Lancet Neurology*, 5(11), 932-936. doi:10.1016/s1474-4422(06)70581-6

Ozakbas, S., Turkoglu, R., Tamam, Y., Terzi, M., Taskapilioglu, O., Yucesan, C., & Turkes, N. (2018). Prevalence of and risk factors for cognitive impairment in patients with relapsing-remitting multiple sclerosis: multi-

center, controlled trial. *Multiple Sclerosis and Related Disorders*, 22, 70-76. doi:10.1016/j.msard.2018.03.009

Thompson, A. J., Banwell, B. L., Barkhof, F., Carroll, W. M., Coetzee, T., Comi, G., ... & Cohen, J. A. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet Neurology*, 17(2), 162-173. doi:10.1016/s1474-4422(17)30470-2

Türk Nöroloji Derneği (TND). (2020). Multipl Skleroz Tanı Ve Tedavi Kılavuzu. In 10 September 2023 retrieved from https://www.noroloji.org.tr/TNDData/Uploads/files/MS_tan%C4%B1%20ve%20tedavi%202018.pdf

World Health Organization (WHO). (2011) Waist circumference and waist-hip ratio: report of a WHO expert consultation, Geneva, 8-11 December 2008. In 16 December 2023 retrieved from https://iris.who.int/bitstream/handle/10665/44583/?sequence=1

Wollin, J., Bennie, M., Leech, C., Windsor, C., & Spencer, N. (2005). Multiple sclerosis and continence issues: an exploratory study. *British Journal of Nursing*, 14(8), 439-446. doi:10.12968/bjon.2005.14.8.17926