The relationship between obesity, sex difference, and fatigue in patients with multiple sclerosis

Obesity, sex difference and fatigue in patients with multiple sclerosis

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Abstract

Aim: Obesity is a risk factor for autoimmune disorders and worsens the disease process. The purpose of this study was to investigate the association between the body mass index (BMI), sex differences and fatigue in MS patients compared to healthy controls. Material and Method: Our study consisted of 59 MS patients (37 females, 22 males) and 45 healthy controls. Medical history of MS patients, including the duration of illness, BMI, Fatigue Severity Scale (FSS) number of annual episodes, demographic data (sex, age) and BMI and fatigue severity of healthy control group were recorded. Results: The female MS patients had a significantly higher mean BMI than the control group and a significant positive correlation between BMI and Extended Disability Scale Score (EDSS) and fatigue. There was no significant difference between the male MS patients' BMI and that of controls. Obese MS patient group had a significantly higher mean fatigue level than the normoweight and overweight ones and significantly higher mean annual attack number than the normoweight MS group. In the female MS patients group, the mean BMI and EDSS of Fatigue Severity Scale (FSS) ≥4 group were significantly higher than of FSS <4 group but there was no significant correlation between the FSS ≥4 and FSS <4 groups in the male MS patients. Discussion: These findings suggest that being obese in MS patients may affect attacks via inflammatory pathway as well as disability, particularly so in women; they also show the necessity of approaches encouraging weight loss for MS treatment

Keywords

Obesity; Sex Differences; Fatigue; Multiple Sclerosis

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Introduction

Multiple sclerosis is an autoimmune disease of the central nervous system in the presence of demyelination, inflammation, and neurodegeneration [1]. Obesity is a risk factor for autoimmune disorders. In obese individuals, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) secretion increases in proportion to obesity severity [2]. Among patients with multiple sclerosis (MS), being overweight in the adolescent period, particularly in female patients is considered as a risk factor for MS development [3]. Munger KL et al. in a prospective cohort study, found that a body mass index (BMI) of ≥30 at the age of 18 was associated with a more than 2 times increased MS risk [4]. Furthermore, obesity is known to worsen the disease process in some autoimmune disorders [5]. Lipoidosis stimulates a proinflammatory macrophage profile in the fatty tissue, and an experimental autoimmune encephalomyelitis model using this macrophage profile in mice showed a greater rate of recurrence [6,7]. It has been reported that among overweight and obese MS patients the chance of getting full remission and ''No evidence of disease activity (NEDA)" condition during interferon beta treatment is less [8].

It is generally well known that being overweight exerts a negative impact on activity in the general society [9]. It has been reported that in obese patients systemic inflammation may reach brain causing local inflammation in some brain regions and that comorbid conditions such as fatigue may develop at the end of that process [10,11]. Moreover, fatigue is one of the most common symptoms among MS patients.

In the light of these data, we aimed to explore the relationship between sex, BMI and fatigue in MS patients.

Material and Method

This study included a total of 59 patients with relapsing-remitting multiple sclerosis (RRMS) who were under interferon or glatiramer acetate treatment at Harran University Faculty of Medicine Department of Neurology and 45 healthy volunteers. The MS patient group met the McDonald criteria for RRMS [12]. The ethics committee approval was obtained by Harran University, Department of Medicine before the beginning of the study. Informed consent was obtained from all individual participants included in the study.

Patients who had an attack within the last 3 months and received steroid treatment, patients who had a severe heart disease, malignancy, a history of medication use with potential effects on weight gain, other psychiatric or neurological disorders, or an Extended Disability Scale Score (EDSS) >4 were excluded from the study. The healthy control group consisted of persons without any chronic systemic disorder.

All patients underwent a neurological examination to determine their EDSS developed by Kurtzke. Fatigue severity was rated using the Fatigue Severity Scale (FSS) [13]. Composed of 9 items, this scale is rated between 1 and 7 points (1 = strongly disagree, 7 = strongly agree), and the total score is calculated as the mean of the 9 items. The patients were divided into 2 groups based on the FSS score: patients with fatigue (FSS score ≥4) and those without (FSS score <4). Body mass index (weight divided by the square of body height (kg / m2) of all participants was calculated. According to the classification by the World Health Organization, normal weight (BMI = 18,5 - 24,9), overweight (BMI = 25 - 29) and obese (BMI ≥ 30). Medical history of MS patients, including the duration of illness, BMI, FSS and number of annual episodes, demographic data (sex, age), BMI and fatigue severity of healthy control group were recorded.

Statistical analysis

Statistical analysis was assessed with Statistical Package for Social Sciences for Windows version 20.0 (SPSS, Chicago, IL, USA) program. The descriptive statistics included mean ± standard deviation, number and percentage. Normally distributed continuous variables were compared using Student's t-test and those without normal distribution with Mann-Whitney U test. The comparison of more than 2 groups was carried out using the Oneway ANOVA for normally distributed variables and Kruskal -Wallis test for non-normally distributed variables. The correlation analysis between variables was performed using Spearman rank correlation coefficient. A p-value of less than 0.05 was considered statistically significant.

Results

The 59 RRMS patients had a mean age of 32,64 ± 8,38 years and a mean disease duration of 6,67 ± 4,85 years. Among RRMS patients there were 37(62.7%) women and 22 (37.3%) men. The female MS patients had a mean age of 31 ± 8,92 years and a disease duration of 6,51 ± 4,6 years. The male MS patients had a mean age of 34,9 ± 6,87 years and a mean disease duration of 7 ± 5,26 years (Table 1).

Table 1. Demographic and clinical parameters of the MS patients.

	Female (n=37)	Male (n=22)	Total (n=59)	P
Age, years	31±8,92	34,9±6,87	32,64±8,38	0,084
Disease duration (years)	6.51±4.60	7.00±5,26	6,67±4.85	0,361
EDSS	2.09±1,06	2.22±0.90	2.14±1.00	0.407
BMI (kg/m^2)	26.37±3.76	25.14±3.90	25.91±3,83	0.235
FSS skoru	4.09±1.61	3.72±4.09	3.95±1.60	0,209
AAN	0.89±1.10	0.90±1.26	0.89±1.15	0,876

The results are shown as mean ± SD (standard deviation). EDSS; Expanded Disability Status Scale, BMI - body mass index; FSS; Fatigue Severity Scale, AAN; Annual attack number, p; difference between females and males

The female MS patients had a significantly higher mean BMI than the control group, but there was no significant difference between the male MS patients' BMI and that of controls (Table 2). The female MS patients had a significant positive correlation between BMI and EDSS and FSS and between EDSS and FSS (p=0.014, p=0.002, p=0.000). The male MS patients had a significant positive correlation between EDSS and FSS, but no significant correlation between BMI and EDSS and FSS (p=0.002, p=0.941, p=0.872). The mean EDSS of MS patients with FSS ≥4 was significantly higher than that of FSS <4. In the female MS patients group, the mean BMI and EDSS of FSS ≥4 were significiantly higher than of FSS<4 but there was no significiant relationship between the FSS ≥4 and FSS <4 groups in the male MS patients (Table 3).

Table 2. Comparison of clinical parameters among the patient groups with control group

	Female (n=37)	Female-C (n=26)	Male (n=22)	Male-C (n=19)	Total	Total-C	p	p1	p2
Age	31.00±8.71	28.0±8.67	34.9±6.87	32.26±8.21	32.64±8.38	30.17±8.57	0.249	0.266	0.158
BMI	26.37±3.76	24.13±2.66	25.14±3.90	24.63±5.31	25.91±3.83	24.34±3.95	0.022	0.521	0.033
FSS	4.01±1.69	2.91±1.32	3.72±1.58	3.19±1.26	3.95±1.60	3.03±1.29	0.002	0.249	0.001

The results are shown as mean ± SD (standard deviation). BMI - body mass index; FSS; Fatigue Severity Scale, Female-C; Female- control, Male-C; Male-control, Total-C; Total- control, p; difference between females and females-control, p1; difference between male and male-control, p2; difference between total and total-control

Table 3. Comparison of clinical parameters between FSS<4 and FSS ≥ 4 groups in MS patients.

	Female		Male		Total		p	p3	p2
	FSS<4	FSS≥4	FSS<4	FSS≥4	FSS<4	FSS≥4			
Age (years)	27.84±7.16	32.91±9.09	33.50±6.53	36.08±6.55	30.30±7.32	33.97±8.57	0.091	0.368	0.082
Disease duration (years)	5.38±4.27	6.64±4.72	8.40±5.03	6.83±5.40	6.69±4.76	6.70±4.88	0.249	0.456	0.907
BMI (kg/m2)	24.64±1.79	27.31±4.23	25.70±4.21	24.68±3.74	25.10±3.05	26.43±4.21	0.011	0.561	0.165
EDSS	1.26±0.43	2.54±1.04	2.15±1.29	2.29±0.450	1.65±0.99	2.45±0.88	0.000	0.159	0.000

The results are shown as mean ± SD (standard deviation). BMI - body mass index; FSS; Fatigue Severity Scale, p; difference between female FSS<4 and FSS ≥4, p1; difference between male FSS<4 and FSS≥4, p2; difference between total FSS<4 and FSS≥4

Table 4. Comparison of clinical parameters among the MS patients in different BMI groups.

	Normal (n=25)	overweight (n=22)	obese (n=12)	p	p1	p2	p3
Age (years)	30.28±7.71	33.59±7.90	35.33±8.74	0.153	0.339	0.179	0.817
Disease duration (years)	5.08±4.27	7.95±4.88	7.79±5.05	0.039	0.026	0.045	0.929
FSS	3.74±1.70	3.61±1.50	5.02±1.16	0.005	0,798	0.002	0,005
EDSS	1.96±0.88	2.09±1.03	2.62±1.10	0.225	0.810	0.089	0,191
AAN	0.44±0.76	0.95±1.29	1.58±1.31	0.025	0.211	0.013	0.157

The results are shown as mean ± SD (standard deviation). EDSS; Expanded Disability Status Scale, BMI - body mass index; FSS; Fatigue Severity Scale, AAN; Annual attack number AAN; Annual attack number, P : within groups; p1; difference between normal and overweight, p2; difference between normal and obese, p3; difference between overweight and obese

Similarly, obese MS patient group had a significantly higher mean fatigue level than the normoweight and overweight ones and annual attack number than the normoweight MS group. Whole MS group and female MS groups had a significantly higher mean fatigue level compared to the controls (Table 4).

Discussion

Among MS patients, being overweight or obese cause disease progression as well as fatigue and pain through immune dysfunction [4,14]. Ghadirian et al. reported that BMI was significantly higher in MS patients compared to controls; furthermore, female MS patients had a significantly higher BMI compared to the controls, whereas, there was no significant difference for BMI between male MS patients and controls [15]. A recent study by Bove et al. demonstrated a significant association between higher BMI and worse EDSS in female MS patients. In contrast, there was a significant relationship was found between higher BMI and lower EDSS in male MS patients [16].

In accordance with the literature (50-70%), 57,6% of our study population was overweight and obese [14,17]. The mean BMI of the female MS patient group was significantly higher than that of the healthy control group but there was no significant difference between male MS patients and healthy controls. In addition, there was a significant positive correlation between BMI and disability and fatigue among female MS patients, whereas their male counterparts did not have such a correlation.

The correlation between fatigue, one of the most common symptoms in multiple sclerosis, and disability was shown by previous studies [18,19]. In contrast, several other studies have denied a correlation between age, disease duration, and sex [20,21]. In accordance with the literature reports, a positive correlation was detected between disability and fatigue in both male and female MS patients. Similarly, MS patient group was more fatigued than the control group. In the female MS patients group, the mean BMI and EDSS of FSS ≥4 group were significantly higher than of FSS <4 group but there was no significant correlation between the FSS ≥4 and FSS <4 groups in the male MS patients. We did not detect any significant correlation between fatigue and disease duration, age, and sex.

Obesity is commonly associated with fatigue. It has been reported that there is an association between increased cytokines, especially IL-6, and fatigue in obese patients [4]. In our study, there was a positive correlation between FSS and BMI among women but men did not have such a correlation; the mean fatigue level of the obese patient group was significantly higher than that of the normoweight and overweight patient group. A study by Peddy et al. reported that, comparing to normoweight MS patients, obese MS patients had 2 times more relapses [22]. In contrast, a recent study failed to demonstrate a significant correlation between higher BMI and the yearly number of attacks, disease duration, and EDSS scores [23]. We found significantly higher mean annual attack number in obese MS patients compared to the normoweight MS group.

There is a stronger association between inflammatory parameters and obesity in women than in men. It has been suggested that this result may be related to the different distribution of body fat tissue in women and the difference in sex hormones [24]. Abdominal obesity is particularly more common among women and inflammatory parameters such as CRP, IL-6, TNF-6 have been reported to be higher in women with abdominal

obesity compared to those without [25]. These findings suggest that obesity may affect inflammatory pathways in the pathogenesis of MS, with a more prominent correlation in the female MS patients potentially attributable to abdominal obesity being more effective on proinflammatory pathways.

The small patient groups and the absence of an assessment of abdominal obesity were our study's limitations.

Conclusion

This study showed that mean BMI of female MS patients was greater than that of healthy controls, and that these patients were more fatigued than the healthy controls. Furthermore, MS patients had a significant positive correlation between BMI and EDSS in the female MS patients. It was observed that fatigue, disability and mean annual attack number were significantly higher in obese patients than in the normoweight MS patients. These findings suggest that being obese in MS patients may affect attacks via inflammatory pathway as well as disability, particularly so in women; they also show the necessity of approaches encouraging weight loss for MS treatment. There is a need for prospective studies examining the relationship between BMI and inflammatory biomarkers in larger patient groups, where more regional assessments, such as those of waist and hip circumference, are done.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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