



The Effects of Body Mass Index (BMI) on Multiple Sclerosis (MS) Progression

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Abstract

Objective: To evaluate the association between Body Mass Index (BMI) and Multiple Sclerosis (MS) Progression as measured by the Expanded Disability Status Scale (EDSS), Magnetic Resonance Imaging (MRI) new lesions, relapse rate, and the Timed 25 Foot Walk (T25FW).

Methods: Subjects (n=150) were identified through age, gender, race, and disease duration and followed retrospectively for 5 years based on medical records. Logistic regression analysis was performed to determine the association between BMI and MS progression.

Results: The mean age was 45.5 years, 79% were females and the mean BMI was 27. The odds of having increased EDSS by at least 1 point in obese patients with mild disability was 8 times greater than those with normal BMI ($p=0.017$). The odds of having new brain MRI lesions was 6.2 times greater in overweight subjects ($p<0.0001$) and 2.6 times greater in obese subjects ($p=0.048$) than in subjects with normal BMI. The odds of having at least 1 relapse in 5 years was 3.8 times ($p=0.040$) in obese subjects than non obese. The odds of having 20% change on the T25FW was 1.1 ($p=0.047$). African Americans had 5 times greater odds to have higher disability ($p=0.015$) than Caucasians, and current smokers had 5 times greater odds to have increased disability than never Smokers ($p=0.03$).

Conclusions: BMI has an important role in MS outcomes. Assessment and addressing a plan of care with dietary guidelines and weight control programs for patients with MS aid in minimizing the progression of the disease.

Introduction

Overweight status and obesity, inflammatory processes, influence the progression of chronic inflammatory diseases such as MS. MS, an autoimmune disease, is a progressive disease with slow or relatively rapid deterioration of neurologic functions [1-3]. Although BMI is a modifiable risk factor, 65% of American adults are overweight or obese. Obesity is a growing epidemic that affects women more often than men [4]. The combined United States prevalence of overweight status and obesity in women over the age of twenty years is 51% [4]. MS and high BMI have serious short and long-term physical and psychosocial implications.

Conflicting limited evidence is available about the relationship between BMI and MS. Longitudinal analyses and cross-sectional studies have suggested that BMI does not have a strong effect on MS disease severity as estimated by self-reported instruments [5]. In addition, an online platform MS research showed a modest correlation between BMI and the course of the disease [5]. Contrarily, a North American Research Committee on MS (NARCOM) data base of 4,500 subjects with MS from 2004-2010 has shown no clear association between BMI and disability as reported by patients [6]. Latest studies have shown increased risk for development of MS in people that were obese during their childhood [7]. Others have shown that obesity was associated with increased risk of MS in girls but not in boys [8]. However, an older study performed in Montreal during the years 1992-1995 with 197 cases of MS and 202 controls showed an inverse relationship between high BMI and the risk of MS [9]. Therefore, additional studies are required to clarify the association between BMI and MS.

Materials and Methods

Purpose and specific aims/objectives of this study

1. Describe the prevalence of the different BMI levels in adult patients with multiple sclerosis.
2. Describe the prevalence of disease progression as measured by the EDSS, MRI burden of

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disease, relapse rate and the 25FW in patients with MS.

3. Determine the relationship between BMI in adult patients with MS and severity of MS as measured by the Expanded Disability Status Scale (EDSS), the MRI changes, relapse rate, and the 25 Foot-Walk (25FW).

4. Determine the relationship between level of disability in adult patients with multiple sclerosis as measured by the Extended Disability Status Scale (EDSS) and BMI categories or as continuous variable.

5. Determine the relationship between the burden of lesions in adult patients with multiple sclerosis as measured by the MRI films (T2 lesions & Gadolinium enhancing lesions) and BMI categories or as a continuous variable.

6. Determine the relationship between relapse rate within one and five years in adult patients with multiple sclerosis and BMI categories or as a continuous variable.

7. Determine the relationship between the timed 25-foot walk in adult patients with multiple sclerosis as measured by the average between two-timed 25-foot walk and BMI categories or as a continuous variable.

8. Describe the correlation between BMI indices and demographic factors: age, gender, type of disease course (relapsing vs. progressive pattern), and progression of disease.

Research design

Setting: This study was conducted in an urban neurology academic outpatient center located in a large metropolitan hospital in the Northeastern region of United States. This study was based on review of multiple medical records obtaining demographic details and data about BMI and MS disease progression. The clinic sees approximately 4,500 MS patients annually. The medical team in the MS center includes multiple internal experts in MS. The prevalence of MS is extremely high in the center's Metropolitan area [9].

Sample:

Subjects' inclusion criteria: Medical records review criteria for all male and female subjects included the following: 1) have multiple readings of BMI 2) have a diagnosis of multiple sclerosis, 3) have any type of MS (relapsing remitting, secondary progressive, progressive relapsing or primary progressive), and 4) any duration of disease 5) have at least 2 MRI at least one year interval, 6) have a few 25FW records, 7) have a full neurological exam to estimate EDSS score, 8) any years of age, 9) be of any ethnic group.

Subjects' exclusion criteria: The following records were excluded: 1) those with probable or possible MS, 2) those diagnosed with the variant forms of MS; Transverse myelitis, Neuro Myelitis Optica (NMO), Behcet disease, Marburg disease, balo's concentric disease or Acute Disseminated Encephalomyelitis (ADEM), 3) those with other uncontrolled inflammatory immune mediated diseases 4) those without measures of BMI and other required parameters.

Sample size and power calculation: A power level of 0.80 was chosen to determine the sample size in this study. The alpha chosen for this study is 0.05. The effect size chosen for this study is low to moderate effect based on the prevalence of high BMI in MS in a few studies and the potential association between BMI and MS. Based on these characteristics, G-Power instrument, and the statistical tests to

be used, a sample size of 150 subjects was chosen [10,11].

Variables and instruments

BMI: BMI is calculated as weight (kg)/height (m²). BMI is not a perfect measure of adiposity because it is affected by age and ethnicity. The ratio of fat-free mass to height begins to decrease after age 45 years, especially among women.

EDSS change: The EDSS (Appendix B) is an ordinal clinical rating scale that summarizes a neurologic examination, which provides a measure of overall disability of MS [12]. The EDSS is a 20-item scale, ranging from 0 (normal examination) to 10 (death due to MS) in 0.5-point increments. The EDSS combines impairment and disability by incorporating the scores of eight functional systems [12-14]. A change of at least one point for EDSS <6.0 and 0.5 points for EDSS >6 are considered clinically significant [15].

The EDSS has a fair to substantial inter-rater reliability reported as kappa coefficient score of 0.32 to 0.76 [16]. Studies have shown that inter and intra-rater reliabilities of the functional system scores were high with kappa coefficients ranging between 0.42 and 0.66, and intra-class correlation coefficients ranging between 0.67 and 0.92 [14].

The validity of the EDSS was confirmed by its high correlation with the Scripps Neurological Rating Scale (SNRS) at 0.92, and with the functional independence measure at 0.87. A change of at least one point for EDSS <6.0 and 0.5 points for EDSS >6 are considered reliable [15]. The EDSS is not useful in detecting small clinical changes.

T25FW: The T25-FW is a quantitative mobility and leg function performance test based on a timed 25-walk. The 25FW is measured twice during each follow-up visit. Patients may use an assistive device during the walk. The task is completed twice and the score for the T25-FW is the average of the two completed trials. Several approaches have been done to define a significant change in the timed 25-foot walk (T25FW) for patients with MS. Researchers defined a significant change in the T25FW of 3 seconds prolongation of patients with MS that had a score of 3.5 or less on the EDSS instrument Kurtzke [13,17].

Others suggested that an increase of more than 20% in the T25FW indicate a significant change in gait. The limitations of the T25FW include participants' prior exposure to the test, participants' variability related to disease type and disability, and variability in researchers administrating the T25FW test [18,19]. Furthermore, multiple studies have shown that a change of 20% or above 20% in the T25FW had a meaningful effect on patients' life [20,21]. For example, a 28% change has led to occupation change due to MS.

MRI change: MRI is a non-invasive method for assessing pathological changes within the central nervous system (CNS). It is used increasingly for diagnosis, and as an objective biological marker of disease activity in MS. Although the relationship between MRI measures and clinical outcomes is not robust, MRI changes are used as clinical markers of disease progression. However, multiple studies have shown that increase in lesion load and activities are correlated with acute relapses and disease progression in MS [22]. Increased MRI signals can reflect a range of pathological changes from acute inflammation to remarkable tissue loss. Furthermore, brain lesions at baseline have predictive value toward long-term disability [23].

The Demographic Form: The Demographic form developed by the investigator, included questions about the characteristics of the subjects enrolled in the study including age, sex, race, marital status,

Table 1: Descriptive Statistics.

Variable	Control (No MS progression) n = 96		Cases (+MS Progression) n = 54	
	Mean/n	SD/%	Mean/n	SD/%
Total n=150				
Age	47.66	14.14	41.92	13.95
Education in years	15.71	2.56	15.04	2.75
Duration of disease	11.29	9.44	11.85	9.63
Gender / female	74	49%	40	27%
Ethnicity / White	55	37%	32	21%
Smoking / Never-smokers	64	42%	36	24%
Number of MS relapses 1	0.29	0.64	0.76	0.95
Number of MS relapse in 5	1.66	1.31	2.74	2.52
EDSS at onset of study	2.68	2.36	2.89	2.34
EDSS at 5 years	3.01	2.56	3.36	2.39
BMI at onset of study	27.13	6.32	27.66	8.07
BMI at end of 5 years	27.28	6.43	27.65	8.13
25 Foot-Walk at onset	8.49	11.48	5.57	2.98
25 Foot-Walk at 5 years	6.74	7.64	6.63	6.35

vitamin D level, smoking history, alcohol intake, employment status, and social status (Appendix D). In addition, the demographic form included the disease history; disease duration, type of MS, use of disease modifying agent for MS, progression of disease, EDSS, 25 foot-walk measures, number of MS relapses, brain and spine MRI activity, and annual BMI measures. Furthermore, change was identified for each participant for the 25 foot-walk, BMI, EDSS, Brain MRI and spine MRI along of the 5-years study participation retrospectively.

Procedure: Collection of data was obtained from chart review from 1/1/2005-3/31/2014. The data included demographic and disease related variables.

Data management: Data were analyzed using the Statistical Package for the Social Sciences statistical software package version 18.0 (SPSS/PASW statistic 18) (SPSS Inc., Chicago, IL, USA). To identify errors, data was entered twice into two separate files. In any type of report that would be published, there was no information that will make it possible to identify any of the participants.

Statistical analysis

Descriptive statistics were used to analyze the demographic data and to describe the sample characteristics. The association between the BMI and MS disease progression as measured by EDSS change, 25-foot walk change, relapse rate and MRI changes as evident by increased number of lesions was conducted using logistic regression.

Bivariate and multivariate analyses using two-tailed tests of significance ($p < 0.05$) were conducted to examine the relationships between BMI and a series of variables, including age, gender, education, occupation status, and marital status. In addition, Spearman's rank order correlation, Kruskal-Wallis and Mann-Whitney analyses were used to assess relationships between BMI groups and other variables. These statistical tests were used because the distribution of the variables did not follow a normal distribution.

Protection of human subjects

Approval for this study was obtained from the Institutional Review Board (IRB) of Mount Sinai Hospital and from Columbia University's Human Subjects Research Review Committee. Computerized data for analysis was identified by subjects' numbers only.

Results

Sample characteristics

The mean age was 45.5 years. The majority of participants were female (76%) and Non-Hispanic-White (58%). 50% of the participants were married living with their family. 53% were working full time and 49% of the participants had college education. The most common type of MS was relapsing-remitting MS (RRMS) (77%). 82% of the participants had no family history of MS. 36% of the participants had progression of their MS disease. The 5 years mean relapse rate was 2.2. Most of the participants had longer duration of MS disease (70% >5years). The mean of disease duration was 11.35 years. The mean EDSS disability score was 2.8 while 25% had an EDSS >4 and 75% had EDSS \leq 4. 22% of the participants in this study were not on a disease-modifying agent. Majority of the participants were overweight (31%; 25 to 29.9) or obese (17%; 30 to 39.9) and severely obese 8% (\geq 40) (Table 1).

Research questions

1. What is the prevalence of the different BMI levels among patients with MS?

The prevalence of overweight and obesity in this study was high (56%).

2. What is the prevalence of progression of MS based on the EDSS, MRI changes, relapses, and 25 Foot-Walk?

The prevalence of progression of the MS disease was 36% (n=54) and 64% (n=96) without MS progression. 70% had EDSS \leq 4 and 30% had EDSS >4. 39% had increased disability by 0.5 to 1.5 points on the EDSS scale, 2.7% had increased EDSS by 2 points or more, 0.7% had improvement on the EDSS and 57.7% had no change on the EDSS scale. 25% had 20% changes or above on the 25 foot-walk and 24% had less than 20% change on the 25FW, and 44% had no change. The progression based on radiological activity was 47% on the brain MRI and 28% on the spine MRI. 30% had 1-3 relapses in the last year of the study while 19% had 1 relapse. 33% of the participants had 1 to 3 relapses in the 5 years of the study and 27.3% had 1 relapse throughout the 5 years of the study.

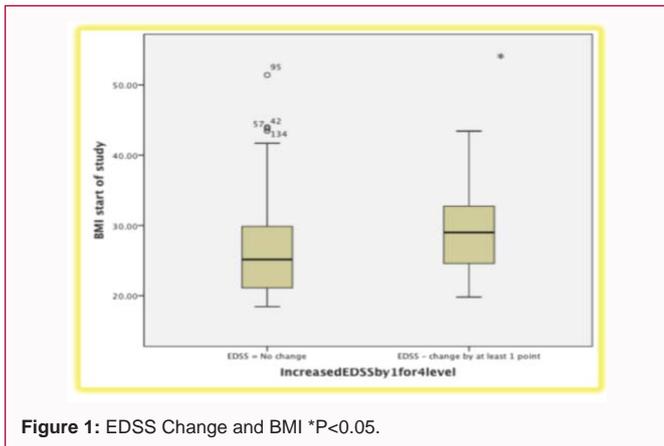


Figure 1: EDSS Change and BMI * $P < 0.05$.

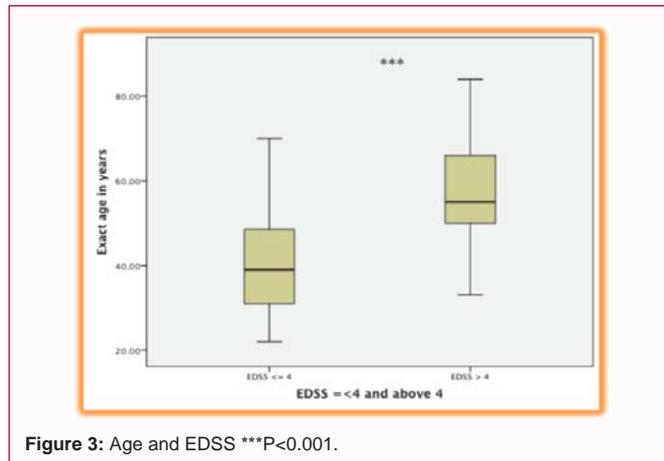


Figure 3: Age and EDSS *** $P < 0.001$.

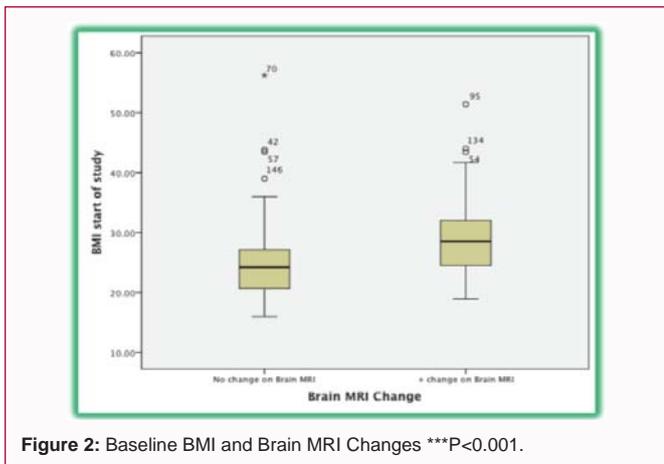


Figure 2: Baseline BMI and Brain MRI Changes *** $P < 0.001$.

3. What is the relationship between initial BMI and MS progression?

There were no statistical significant results between BMI and MS disease progression as a dichotomous variable.

4. What is the relationship between initial BMI and MS progression as measured by the EDSS?

The odds of having increased EDSS by at least 1 point in patients with mild disability (EDSS ≤ 4) that had onset BMI ≥ 30 was 8 times than those that had BMI < 25 with statistical significance of 0.017 controlling for age, gender, ethnicity, disease duration, brain changes, number of relapses in 1 year, and MS type (Figure 1). Additionally, Chi Square analysis demonstrated a statistical significant difference between the EDSS change by at least 1 point in patients with EDSS ≤ 4 within 5 years and the BMI categories (< 25 , 25-29.99, ≥ 30), $X^2 = 6.310$, $p = 0.043$.

5. What is the relationship between initial BMI and MS progression as measured by the MRI changes?

The odds of having brain MRI changes as characterized by enhancing lesions and new T2 lesions was 6.2 in overweight subjects ($p = 0.000$) and 2.6 in obese subjects ($p = 0.048$) than in subjects with normal BMI controlling for age, gender, EDSS, number of relapses and disease duration (Figure 2). There was a significant difference between the initial BMI and brain MRI changes (Kruskal-Wallis $X^2 = 13.75$, $p = 0.000$). Post-Hoc Mann-Whitney analysis showed that patients with brain MRI changes ranked 88.31, and patients without brain MRI changes ranked 61.99 ($u = 1825$, $p = 0.000$). In addition the

Spearman correlation between BMI and brain MRI changes was 0.304 ($p = 0.000$).

6. What is the relationship between initial BMI and MS progression as measured by relapse rate?

The odds of having at least 1 relapse in 5 years is 3.8 times ($p = 0.040$) in subjects with BMI ≥ 30 than those with BMI < 30 controlling for gender. There was no association between BMI and relapse rate within the last year of the study.

7. What is the relationship between initial BMI and MS disease progression as measured by the Timed 25 Foot-Walk?

The odds of having 20% change on the 25-foot walk is 1.1 ($p = 0.047$) times for each increase of one unit of the BMI controlling for age, gender and disease duration. There was a significant difference in the number of people who had change of 20% in the 25FW across the 3 BMI groups (Kruskal-Wallis $X^2 = 6.859$, $p = 0.032$). Severely obese (BMI ≥ 40) was significantly different than both non obese (< 30) ($p = 0.01$) and obese (30 to 39.99) ($p = 0.02$) (Mann-Whitney Post-Hoc).

8. Is there a relationship between demographic variables and BMI and progression of MS disease?

Age was correlated with EDSS (Figure 3). The Spearman correlation was 0.534 ($p < 0.001$). Non-Hispanic Blacks with MS had 5 times the odds of having higher EDSS than Non-Hispanic Whites controlling for age, duration of disease and BMI ≥ 25 ($p = 0.015$). In addition, Non-Hispanic Blacks ($p = 0.000$) and Hispanic ($p = 0.019$) were significantly different than Non-Hispanic whites in relation to BMI measures. There was a significant difference between BMI and gender (Kruskal-Wallis $X^2 = 4.9$, $p = 0.026$). Females ranked higher therefore, the BMI was higher in Females than males (Mann-Whitney $U = 1550$, $p = 0.028$).

Discussion

Prevalence of BMI and MS disease progression

The prevalence of overweight and obesity in this study is high. The majority of the participants were overweight ($n = 48$, 32%; baseline BMI = 25 to 29.9) or obese ($n = 43$, 29%; baseline BMI ≥ 30). The total overweight/obese percent in the study was 60% similar with the magnitude of the obesity epidemic in the general population. Furthermore, the distribution of BMI in other studies was similar to our investigation. Pilutti et al. [24,25] had 52 (31.0%) participants that were classified as normal weight; 61 (36.3%) participants were

classified as overweight; and 55 (32.7%) participants were classified as obese totaling 69%. Another study has shown a more similar distribution to our investigation, over 50% of participants were classified as overweight (BMI=25.0 kg/m² to 29.9 kg/m²) or obese (BMI ≥ 30.0 kg/m²) [25].

Less than half of the patients (39%) with MS had disease progression, which is lower than the progression of disease among overall patients with MS. The majority of the patients (70%) had mild disability as measured by the EDSS scale (EDSS ≤ 4). Almost 20% have changed by at least 1 point on the EDSS among those with EDSS ≤ 4 (n=18 out of 108). In a few studies patients with MS with EDSS ≤ 4 have shown worsening by 1-1.5 points on the EDSS scale within 5 years and those with higher EDSS have shown worsening by 0.3 to 0.7 points within 5 years [2].

Relationship between BMI & MS progression

BMI and EDSS: BMI of 30 or above 30 was predictive of increased EDSS by at least 1 point in patients with mild disability (EDSS ≤ 4) over the course of 5 years retrospectively. Similarly, Tettey et al. [26] have shown that higher BMI was independently associated with higher EDSS (p=0.013). Alternatively, Pilutti et al. [24,25] study has shown that there were no significant correlations between BMI and Patient Determined Disease Steps (PDDS patients' reported scale) for any of the three time points (p>0.05), baseline, 12 months and 24 months. Path analysis indicated a minimal and inconsistent impact of BMI on the change in PDDS over time, and PDDS had a minimal and inconsistent influence on change in BMI. This study has used patients' reports (mailed questionnaires) about their disability status and BMI parameters, which might lead to bias in their study. Furthermore, they have included in their analysis patients with mild to moderate disability.

BMI and MRI: This study has shown a highly significant difference between the baseline BMI as continuous variable and brain MRI changes within 5 years (Kruskal-Wallis Chi Square =13.75, p=0.000). Furthermore, the odds of having brain MRI changes as characterized by gadolinium enhancing lesions and new T2 lesions was 6.2 in overweight subjects (baseline BMI 25 to 29.99) (p=0.000) and 2.6 in obese subjects (baseline BMI ≥ 30) (p=0.048) than in subjects with normal BMI controlling for age, gender, EDSS, number of relapses and disease duration. A study with 326 RRMS patients, 163 patients with progressive MS, 61 patients with CIS and 175 age and sex matched healthy controls has shown an association between BMI and MRI increased lesion volume [27]. It has demonstrated a significant increased T2 lesion volume in RRMS patients who had hypertension, heart disease and obesity (p=0.028) [27]. This study confirms the current investigation finding a highly statistical significance between high BMI and increased burden of disease seen on MRI.

BMI and Relapses: The odds of having at least 1 relapse within 5 years was 3.8 times (p=0.040) in subjects with BMI ≥ 30 than those with BMI < 30 controlling for gender and smoking history in this retrospective study in patients with all types of MS (RRMS=71%, SPMS=23%, PPMS=5%, PRMS=1%). There was no association between BMI and relapses within one year of the study. Consistently, Tettey et al. [28] have demonstrated that BMI was not associated with the hazard of relapse in MS in a prospective cohort study of 141 participants with relapsing-remitting MS followed from 2002 to 2005.

BMI and 25 Foot-Walk (25FW): The current investigation has shown a significant difference between BMI and at least 20% change

on the 25FW over the course of 5 years. Other studies have not focused on change of the 25FW but on the performance of the walk. For example, there was no significant impact of BMI on outcomes of mobility in a 7 day study [24]. The lack of an effect of weight status on mobility in short studies emphasizes the need to do longitudinal cohort studies and in addition to identify other factors, which may be important targets of ambulatory performance in persons with MS [24].

Additional analyses

Non-Hispanic Blacks with MS have the odds of having higher EDSS, 5 times (p=0.015) than Non-Hispanic Whites controlling for age, duration of disease and BMI ≥ 25. Consistent evidence of more disability in African Americans compared with whites was found in multiple studies, although subgroups were often too small to establish statistical significance. African Americans had a higher mean expanded disability status scale score than whites and African Americans reported limb weakness as a presenting symptom of multiple sclerosis more frequently than did whites [29]. In summary, more African Americans than whites experience pyramidal system involvement early in multiple sclerosis, leading to greater disability as measured by the EDSS.

This study has shown a significant predictability of worsening of the disease by smoking. Current smokers had higher odds of having increased EDSS and relapse rate than never smokers. The odds of having an increased EDSS by at least one point was 5.4 times in current smokers (p=0.03) than never smokers. In addition, the odds of having at least one relapse in one year was 4 times in current smokers than in never smokers (p=0.034).

Other studies have shown similar results. The risk of reaching EDSS 4 and 6 in ever smokers compared to never-smokers was 1.34 (with 95% CI: 1.12-1.60) and 1.25 (with 95% CI: 1.02-1.51) respectively [30]. Similarly, current smokers showed 1.64 (95% CI: 1.33-2.02) and 1.49 (95% CI: 1.18-1.86) times higher risk of reaching EDSS scores of 4 and 6 compared with non-smokers [30]. Their data and this study suggest that regular smoking was associated with more severe disease and faster disability progression.

Strengths of the study

This study has significant strengths including a longer retrospective study assessing different parameters for 5 years. The investigation of the disease progression, the dependent variable, relied on multiple assessments; the EDSS, MRI changes, Relapse rate and the 25 foot-walk. In addition, the study had the capability to adjust for relevant and multiple confounders that might have affected the relationship between BMI and MS progression of disease. The demographic variables' frequencies such as, race/ethnicity, mean age and gender, and type of MS were similar to the general MS population promoting the ability to generalize the results. The findings of this study promote decreasing BMI into the healthy range and significantly reducing accumulation of disability.

Limitations of the Study

This study was a retrospective case-control study based on chart review, which does not allow for getting all the information needed for the study. Some information was missing in the chart of the patients enrolled therefore this might affected the results. In practice, case-control studies are often affected by selection bias. Selection bias may have been present in this study, since charts that did not

have BMI readings were excluded from the study upon screening the charts. The BMI was unknown at the onset of the disease, therefore this may affected the results although the study has controlled for multiple confounders including duration of disease.

One of the other limitations is related to BMI as a marker for fat mass. BMI does not distinguish between weight associated with muscle and weight associated with fat. This study did not include waist circumference or waist-to-hip ratio because the data was not available in the medical records. Furthermore, inter-rater reliability of the 25 FW might lead to systematic error due to the high number of clinicians measuring the 25FW (7 clinicians). The EDSS calculation was based on the medical records, which was estimated by each clinician at the center.

Implications for Clinical Practice

Weight status and BMI have emerged as a correlate of disability status in cross-sectional studies and a few cohort studies of persons with MS and represent a possible modifiable predictor of disability progression over time. Mostly, natural history studies have typically focused on non-modifiable factors as predictors of disability and disease progression in multiple sclerosis. Many patients with MS are motivated to change their lifestyle and addressing the modifiable risk factors of their progressive disease. Counseling and nutritional advice may control the BMI in patients with MS and may affect and delay their disease progression.

Future Research

Prospective and longitudinal cohort studies are required to confirm the relationship between BMI and progression of disease as characterized by disability, MRI increased burden of disease, relapse rate and mobility. Furthermore, the study would be more robust if it would include only newly diagnosed patients with MS following their BMI and disease progression over a few years.

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