Impact of Nutritional Intake on Function in People with Mild-to-Moderate Multiple Sclerosis

Lacey Bromley, PT, DPT, NCS, MSCS; Peter J. Horvath, PhD; Susan E. Bennett, PT, DPT, NCS; Bianca Weinstock-Guttman, MD, PhD; Andrew D. Ray, PT, PhD

Background: We sought to assess the associations between nutrition and ambulation, daily activity, quality of life (QOL), and fatigue in individuals with mild-to-moderate disability with multiple sclerosis (MS).

Methods: This cross-sectional pilot study included 20 ambulatory adult volunteers with MS (14 women and 6 men; mean ± SD age, 57.9 ± 10.2 years; mean ± SD Expanded Disability Status Scale score = 4.1 ± 1.8). Primary outcome variables included dietary assessment and the 6-Minute Walk Test (6MWT). Secondary measures included the Timed 25-Foot Walk test, Timed Up and Go test, daily activity, and three self-report questionnaires: the 12-item Multiple Sclerosis Walking Scale, the 36-item Short Form Health Survey (SF-36), and the Modified Fatigue Impact Scale.

Results: Significant correlations were seen between the percentage of diet comprising fats and the 6MWT ($r = 0.51$, $P = .02$) and the physical functioning component of the SF-36 ($r = 0.47$, $P = .03$). The percentage of carbohydrates was significantly correlated with the 6MWT ($r = -0.43$, $P = .05$), daily activity ($r = -0.59$, $P = .005$), and the physical functioning component of the SF-36 ($r = -0.47$, $P = .03$). Cholesterol, folate, iron, and magnesium were significantly positively correlated with the physical functioning component of the SF-36 and the 6MWT.

Conclusions: These findings indicate better ambulation, daily function, and QOL with increased fat intake, decreased carbohydrate intake, and increased intake of the micronutrients cholesterol, folate, iron, and magnesium in people with mild-to-moderate MS. This pilot study highlights the potential impact of diet on function and QOL in MS. *Int J MS Care.* 2019;21:1-9.

Multiple sclerosis (MS) is an immune-modulated disease characterized by inflammation and demyelination of the central nervous system.[1] Symptoms of MS include weakness, spasticity, abnormal sensation, decreased coordination, impaired mobility and ambulation, depression, and fatigue. Lifestyle modification, including dietary intake, has been gaining popularity to reduce the impact of these symptoms.[2]

From the Department of Rehabilitation Science (LB, SEB, ADR), Department of Exercise and Nutritional Sciences (PJH), and Department of Neurology (BW-G), University at Buffalo, The State University of New York, Buffalo, NY, USA. *Correspondence:* Lacey Bromley, PT, DPT, NCS, MSCS, Department of Rehabilitation Science, University at Buffalo, The State University of New York, Buffalo, NY 14214, USA; e-mail: lbromley@buffalo.edu.

DOI: 10.7224/1537-2073.2017-039

The etiology of MS is not fully understood, but there is a consensus that the complex interaction of genetic influences, underlying dormant virus, and environmental or modifiable factors are causative agents in the disease process. Modifiable factors, including sunlight exposure (vitamin D), obesity at a young age, and dietary intake, have been associated with the pathogenesis of the disease process.[3] However, dietary patterns in people with MS have not been extensively studied.

Limited studies have reported that diets with certain macronutrients have correlated with the frequency of MS. For example, the traditional Iranian diet (high in low-fat dairy, whole grains, and meats, including organ meat), the lactovegetarian diet, and the vegetarian diet have all been correlated to a decrease in MS prevalence.[4] Additional studies have identified diets high in fruits and low-fat dairy as protective, whereas diets high in solid fats increased the odds of having MS.[5] Low levels of specific micronutrients, including vitamins D, B_{12}, and A, have also been shown to contribute to the pathogenesis of MS,[6-8] and diets lower in folate and magnesium were found to correlate to increased fatigue in MS.[4]

The number of dietary intervention studies in MS is limited, and such studies traditionally focus on the severity of MS using the Expanded Disability Status Scale (EDSS), magnetic resonance imaging of the brain, and/or relapse rates.[9] Very few dietary studies have used patient-reported outcome measures or standardized gait measures. From those that have, Weinstock-Guttman et al[10] observed improvements in physical and emotional disease burden (36-item Short Form Health Survey [SF-36]) in people with relapsing-remitting MS following a low-fat diet supplemented with fish oil (an omega-3 polyunsaturated fatty acid [PUFA]). A randomized placebo-controlled study of 101 people with MS concluded that a low-fat diet supplemented with vitamin A significantly improved the total score of the Multiple Sclerosis Functional Composite, which includes the Timed 25-Foot Walk (T25FW) test, the Nine-Hole Peg Test, and the Paced Auditory Serial Addition Test. In a follow-up study, after 1 year, fatigue and depression scores were also improved.[11]

Although the EDSS does have a component of gait (4.5-7.0), the psychometric properties have been reported as less than optimal, with low sensitivity, poor reliability, and limited usefulness in assessing walking performance.[12] Improving our understanding of how nutrients affect symptoms such as fatigue-reduced physical activity and walking limitations requires the incorporation of gait measures that reflect endurance (6-Minute Walk Test [6MWT]), gait speed (T25FW test), and functional components (Timed Up and Go [TUG] test). Demonstrating the relationship of improved endurance and gait speed would be beneficial in the prescription of dietary guidelines for people with MS. A recent study evaluated whether a poorer diet—defined as inadequate fruit, vegetable, and whole grain consumption—was associated with performance on the T25FW test and the 6MWT as well as additional comorbidities. The presence of insufficient physical activity and poor diet correlated significantly with reduced functional performance.[13]

Although several observational studies have demonstrated a relationship between specific dietary patterns and the prevalence of MS, very few have shown a correlation of diet with fatigue and quality of life (QOL), and even fewer have correlated nutritional intake with standardized gait measures in people with MS. The purpose of this cross-sectional study was to correlate macronutrient (protein, carbohydrate, fats) and micronutrient intake to ambulation, daily function, fatigue, and QOL in MS. It was hypothesized that diets high in fat and saturated fat would have a negative effect on all the measures.

Methods

Design

This was a cross-sectional study of patients diagnosed as having MS who were recruited through neurology offices across the western region of New York State. All the procedures were approved by the University at Buffalo, The State University of New York, Buffalo, New York, human subjects institutional review board.

Participants

Adult participants (N = 20) of both sexes were recruited as a convenience sample. All the participants provided written consent before enrollment. The inclusion criteria were as follows: a diagnosis of MS, age 20 years or older, and mild-to-moderate disability (EDSS score of 1.0 = no disability, minimal signs in one functional system, to 6.0 = intermittent or constant unilateral assistance and the ability to walk ≥100 m). Degree of disability was established by the patients' neurologists using the EDSS.[14] The exclusion criteria were as follows: evidence of an active disease relapse within the past 30 days, known diabetes, inflammatory bowel disease, dysphagia, impaired cognition that limited ability to complete the questionnaires, and addiction to drugs or alcohol.

Testing Protocol

All the outcome measures were collected on 2 different days separated by a minimum of 1 week. On day 1, participants completed an informed consent form, biometric data, a general health history, and self-report questionnaires and were instructed on the dietary assessments and on wearing the activity monitor. On day 2, participants returned to the laboratory to return the diet assessment forms and the activity monitor. The investigator (L.B.) reviewed the dietary assessments forms with the participant for completeness. All the functional tests were performed on day 2.

The following tests and measures were completed:

The 6MWT

The 6MWT was performed once in an 80-ft hallway according to American Thoracic Society guidelines.[15]

A single-trial 6MWT has been shown to be valid in patients with MS.[16] In brief, patients were asked to walk as fast as they safely could and to cover as much distance as possible within 6 minutes. Assistive devices (canes) were allowed. Total distance covered was recorded.

The T25FW Test

Participants started at a line on the floor and were instructed to "walk as quickly as possible but safely" beyond the second line 25 ft away.[17] Time was recorded in seconds beginning with the first heel strike beyond the start line and the first heel strike after the second line, with the faster time of two trials used for analysis.

The TUG Test

Participants were seated in a chair with two armrests and were instructed to rise from the chair at the word "go," walk as quickly as possible but safely to a mark 10 ft away, turn around, walk back, and sit down. Two trials of the TUG test were performed. The stopwatch was started at the verbal cue "go" and was stopped when the patient was safely seated in the chair.[18] Time was recorded in seconds, with the faster of the two trials used for analysis.

Physical Activity Monitoring

Physical activity was measured using an ActiGraph GT3X+ accelerometer (firmware 1.9.2) (ActiGraph LLC, Pensacola, FL) attached to an elastic belt and worn over the dominant hip for 7 days. Participants were instructed to wear the accelerometers at all times except during swimming and showering. Multiple studies have confirmed that 2 to 7 days is an appropriate wear time to estimate daily expenditure.[19] Evidence suggests that accelerometers such as the ActiGraph GT3X measure both physical activity and walking mobility in people with MS.[20]

Body Fat Percentage Estimation

The participants arrived at the laboratory in a fasted state. The Tanita BC-558 Ironman segmental body composition monitor (Tanita Corp of America Inc, Arlington Heights, IL) was used to assess the bioelectrical impedance of the individual's body. Bioelectrical impedance measures the opposition to the flow of an electric current through the body tissues and can estimate total body water, which is used to calculate body fat percentage.[21]

SF-36: Quality of Life

The SF-36 was self-administered by participants and used to measure QOL using eight subscales: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. Lower scores correlate with decreased performance for all eight subscales.[22]

12-Item Multiple Sclerosis Walking Scale

Participants completed this self-report scale of their perception of their walking ability during the previous 2 weeks. This is an ordinal scale from 1 to 5 for 12 questions related to walking.[23] The best possible score is 12, reflecting no limitations in walking, and 60 is the worst possible score.

Modified Fatigue Impact Scale

The Modified Fatigue Impact Scale was self-administered by participants and used to asses fatigue in terms of physical, cognitive, and psychosocial functioning. Scores are provided for the three subscales as well as a total score. Each item is scored from 0 (never affected) to 4 (almost always affected), and total score ranges from 0 to a maximum of 84. Higher scores indicate greater levels of fatigue.[24]

Dietary Assessment Methods

Three-Day Food Diary. Respondents were asked to record the type and amount of consumed products, dishes, and beverages at the time of consumption on 3 consecutive days (including 1 weekend day) The participants were educated verbally and were provided written directions and examples on how to appropriately record foods and portion size.

Food Frequency Questionnaire. The Food Frequency Questionnaire (FFQ) provides usual intake during the previous 12 months. Participants were asked to quantify the frequency (daily, monthly, yearly) of their intake using standardized serving sizes of 116 food items. The questionnaire was based on the "Block 98" FFQ originally developed by Block et al.[25]

Data Analysis

Participant demographic and clinical characteristics are reported as means, medians, and SDs. Spearman correlation coefficients were calculated to assess associations among nutrient variables, questionnaires, and functional tests. The 3-day food diary and the FFQ were analyzed using Nutritionist Pro software (First DataBank, San Bruno, CA). Macronutrients are expressed as percentage of total calories, and micronutrients are reported as grams per kilogram of body weight. The accelerometers were initialized at a sampling rate of 30 Hz. Files were analyzed at 10-second epochs using the ActiLife 6 data analysis software (ActiGraph LLC). Greater than or equal to 8 hours per day was considered a valid day. Consecutive periods of 60 minutes or more of zero counts (allowing for ≤2 minutes of nonzero counts) were defined as non–wear time and were excluded from the analyses.[26] The Freedson combination algorithm determined average daily physical activity energy expenditure in kilocalories per day.[27,28] For the analysis, data are expressed in kilocalories per kilogram per day to adjust for any differences in energy expenditure due to body mass. A $P < .05$ was used to identify significant results. The analysis was completed using Stata software, version 14.2 (StataCorp, College Station, TX).

Results

Study Participants

As shown in Table 1, the mean ± SD age of the participants was 57.9 ± 10.2 years, and they were primarily female (14 of 20 [70%]). The mean ± SD time since diagnosis was 18.4 ± 11.5 (range, 3-39) years, and the mean ± SD EDSS score was 4.1 ± 1.8 (range, 1.5-6.0). Compared with healthy population norms, the present participants walked a mean ± SD of 378 ± 589 ft less during the 6MWT.[29] The patients in this study were also less active, as demonstrated by the reduced amount of calories expended each day compared with population normative data in similar age groups.[30]

Correlations Between Diet-Reported and Self-Reported QOL Measures

Table 2 summarizes the relationship between the FFQ and the eight subscales of the SF-36. The percentage of saturated fat consumed daily was positively correlated with the physical functioning subscale of the SF-36 ($r = 0.47$, $P = .03$). Similarly, the percentage of carbohydrates consumed negatively correlated with the physical functioning subscale of the SF-36 ($r = -0.47$, $P = .03$). No micronutrient correlations were statistically significant.

Table 3 is a summary of the relationship between the 3-day diet and the eight subscales of the SF-36. Overall, the direction of the relationship between the macronutrients consumed over the 3-day period and QOL were similar to the FFQ findings but did not reach statistical significance. The percentage of saturated fats consumed correlated with vitality, which measures general fatigue/energy ($r = -0.45$, $P = .04$). Different from the FFQ, the 3-day food diary established a direct relationship between cholesterol ($r = 0.63$, $P = .002$), iron ($r = 0.48$, $P = .03$), magnesium ($r = 0.51$, $P = .02$), and folate ($r = 0.62$, $P = .003$) and the physical functioning component subscale of the SF-36.

No significant correlations were found between macronutrient or micronutrient intake (FFQ and 3-day food diary) and the Modified Fatigue Impact Scale (data not shown).

Table 1. Patient demographic characteristics

	Value	Normative data
Sex, F/M, No.	14/6	
Age, y	57.9 ± 10.2	
EDSS score (range)	4.1 ± 1.8 (1.5-6.0)	
Disease duration, y (range)	18.4 ± 11.5 (3-39)	
Disease course, RRMS/SPMS, No.	6/14	
Height, m	1.6 ± 0.01	
Weight, kg	80.0 ± 27.6	
BMI, kg/m^2	27.7 ± 6.5	
Body fat, %	31.9 ± 10.8	
Dietary intake, kcal/d		
FFQ	1531 ± 289.5	
3-Day diary	1702 ± 707.2	
6MWT, ft	1103.4 ± 411.4	1766 ± 314.8[26]
Activity		
Kcal/d	284.6 ± 245.7	680 (524-892)[25]
Kcal/kg/d	12.4 ± 13.2	
% Carbohydrates		
FFQ	49.3 ± 11.1	50%
3-Day diary	51.0 ± 12.8	
% Sugars		
FFQ	23.2 ± 9.4	18%
3-Day diary	19.4 ± 5.7	
% Protein		
FFQ	15.2 ± 3.0	15%
3-Day diary	16.9 ± 3.9	
% Fats		
FFQ	36.2 ± 8.7	30%
3-Day diary	36.5 ± 9.3	
% Saturated fats		
FFQ	11.2 ± 2.5	<10%
3-Day diary	12.2 ± 4.5	

Note: Data are given as mean ± SD or number (range), unless otherwise noted.
Abbreviations: 6MWT, Six-Minute Walk Test; BMI, body mass index; EDSS, Expanded Disability Status Scale; FFQ, Food Frequency Questionnaire; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Correlations Between Nutrient Intake and Functional Measures

Table 4 summarizes the relationship between the FFQ and function. Carbohydrate intake was associated with reductions in distance covered during the 6MWT ($r = -0.43$, $P = .05$) and self-perceived walking ability ($r = 0.46$, $P = .03$) and with less physical activity ($r = -0.59$, $P = .005$). In contrast, diets higher in saturated fats were associated with increased distance covered during the 6MWT ($r = 0.48$, $P = .03$) and shorter TUG test times ($r = -0.48$, $P = .03$). Diets high in total fat were associated with improved 6MWTdistances ($r = 0.51$, $P = .02$), whereas diets high in sugar were associated

Table 2. Food Frequency Questionnaire and quality of life

	SF-36 subscales							
	PF	PH	PE	VT	MH	SF	PN	GH
% Total fat								
r[a]	0.24	−0.02	−0.13	0.03	0.01	0.23	−0.06	0.02
P value[b]	.288	.90	.57	.88	.96	.32	.79	.92
% Saturated fat								
r[a]	0.47[c]	0.04	0.01	−0.07	−0.05	0.38	−0.09	0.16
P value[b]	.03[c]	.84	.94	.74	.82	.09	.67	.49
% Carbohydrates								
r[a]	−0.47[c]	−0.06	0.18	−0.10	−0.40	−0.18	0.10	−0.17
P value[b]	.03[c]	.79	.42	.67	.07	.43	.64	.46
% Protein								
r[a]	−0.11	−0.22	−0.11	−0.02	−0.15	0.19	0.12	0.17
P value[b]	.63	.32	.62	.92	.52	.41	.59	.45
% Sugars								
r[a]	−0.28	−0.05	0.12	−0.03	−0.33	−0.12	−0.19	0.03
P value[b]	.22	.83	.61	.87	.14	.60	.41	.86

Abbreviations: GH, general health; MH, mental health; PE, role limits, emotional problems; PF, physical functioning; PH, role limits, physical health; PN, pain; SF, social functioning; SF-36, 36-item Short Form Health Survey; VT, vitality.
[a]Spearman correlation coefficient score.
[b]Two-sided *P* value, α < .05 was considered significant.
[c]Statistically significant.

with slower T25FW test results (r = 0.43, P = .05) and decreased physical activity (r = −0.51, P = .05).

The relationship between the 3-day diet and functional performance is summarized in Table 5. The 3-day diet analysis also demonstrates a negative correlation between carbohydrate intake and the 6MWT distance (r = −0.45, P = .04), physical activity (r = −0.57, P = .007), and increased time during the T25FW test (r = 0.52, P = .01). The micronutrients cholesterol and folate were correlated with improvements in all functional tests (Table 5). Increased intake of iron was associated with improved 6MWT distance (r = 0.52, P = .01), self-perceived walking (r = −0.47, P = .35), and the TUG test time (r = −0.5, P = .02). Finally, magnesium levels were associated with increases in the 6MWT distance (r = 0.45, P = .04) and physical activity (r = 0.46, P = .03).

Discussion

The results of this pilot study suggest that diets higher in fat and lower in carbohydrates are positively correlated with improvements in ambulation, physical activity, and QOL in people with mild-to-moderate MS; however, no correlations were seen with fatigue. These findings, although demonstrating only a correlation between the variables, begin to highlight the importance of diet in people diagnosed as having mild-to-moderate MS, especially when considering factors contributing to a reduction in function, physical activity, and QOL.

The findings from this study may be somewhat controversial. Previous studies in people with MS have demonstrated that diets high in fat and saturated fat are linked to an increase in disease severity. Swank and Goodwin[31] followed up 150 patients with MS who adhered to a low-fat diet for more than 30 years and determined that diets low in saturated fats were associated with a decrease in disease progression and mortality. However, a recent Cochrane review concluded that because of its observational design, no causation can be determined.[32] At the time of the study by Swank and Goodwin,[31] fat intake was linked to numerous inflammatory conditions, including heart disease and obesity, in the United States. As a result, the US diet began to

Table 3. Three-day food diary and quality of life

	SF-36 subscales							
	PF	PH	PE	VT	MH	SF	PN	GH
% Total fat								
r[a]	0.21	−0.009	0.32	−0.27	−0.20	0.17	0.07	0.05
P value[b]	.36	.96	.16	.24	.39	.46	.76	.81
% Saturated fat								
r[a]	0.11	0.07	0.36	−0.45[c]	−0.23	−0.13	−0.08	0.07
P value[b]	.61	.76	.11	.04[c]	.32	.56	.72	.73
% Carbohydrates								
r[a]	−0.29	−0.14	0.07	−0.09	−0.25	0.10	−0.005	0.11
P value[b]	.03	.79	.42	.67	.07	.43	.64	.46
% Protein								
r[a]	−0.11	0.20	−0.17	0.23	−0.27	−0.003	0.37	−0.41
P value[b]	.62	.38	.46	.32	.24	.98	.10	.06
% Sugars								
r[a]	0.25	−0.12	−0.20	−0.42	−0.03	0.02	−0.11	−0.25
P value[b]	.61	.34	.20	.72	.74	.10	.72	.96
Cholesterol (mg/kg)								
r[a]	0.63[c]	0.12	0.09	−0.16	0.21	0.30	−0.10	0.13
P value[b]	.002[c]	.61	.69	.48	.36	.18	.65	.57
Iron (mg/kg)								
r[a]	0.48[c]	0.30	0.28	−0.23	0.14	0.25	0.17	−0.04
P value[b]	.03[c]	.19	.22	.31	.54	.26	.47	.84
Magnesium (mg/kg)								
r[a]	0.51[c]	0.28	−0.10	−0.01	0.03	0.30	0.26	0.01
P value[b]	.02[c]	.21	.64	.94	.89	.18	.25	.96
Folate (µg/kg)								
r[a]	0.62[c]	0.26	0.11	−0.13	0.08	0.24	0.13	−0.005
P value[b]	.003[c]	.25	.61	.5	.71	.29	.55	.98

Abbreviations: GH, general health; MH, mental health; PE, role limits, emotional problems; PF, physical functioning; PH, role limits, physical health; PN, pain; SF, social functioning; SF-36, 36-item Short Form Health Survey; VT, vitality.
[a]Spearman correlation coefficient score.
[b]Two-sided *P* value, α < .05 was considered significant.
[c]Statistically significant.

Table 4. Food Frequency Questionnaire and function

	Functional measures				
	6MWT	MSWS-12	TUG	ActiGraph data	T25FW
% Total fat					
r[a]	0.51[c]	−0.31	−0.36	0.16	−0.36
P value[b]	.02[c]	.17	.12	.49	.10
% Saturated fat					
r[a]	0.48[c]	−0.34	−0.48[c]	0.15	−0.41
P value[b]	.03[c]	.13	.03[c]	.50	.06
% Carbohydrates					
r[a]	−0.43[c]	0.46[c]	0.43	−0.59[c]	0.41
P value[b]	.05[c]	.03[c]	.06	.005[c]	.06
% Protein					
r[a]	0.03	0.07	0.07	0.00	−0.01
P value[b]	.89	.75	.75	.97	.93
% Sugars					
r[a]	−0.36	0.36	0.37	−0.51[c]	0.43[c]
P value[b]	.10	.11	.11	.02[c]	.05[c]

Abbreviations: 6MWT, 6-Minute Walk Test; MSWS-12, 12-item Multiple Sclerosis Walking Scale; TUG, Timed Up and Go test; T25FW, Timed 25-Foot Walk test.
[a]Spearman correlation coefficient score.
[b]Two-sided P value, $\alpha < .05$ was considered significant.
[c]Statistically significant.

Table 5. Three-day food diary and function

	Functional measures				
	6MWT	MSWS-12	TUG	ActiGraph data	T25FW
% Total fat					
r[a]	0.13	−0.17	−0.21	0.07	−0.21
P value[b]	.56	.47	.36	.76	.35
% Saturated fat					
r[a]	0.28	−0.19	−0.29	0.06	−0.25
P value[b]	.21	.41	.20	.77	.27
% Carbohydrates					
r[a]	−0.45[c]	0.33	0.40	−0.57[c]	0.52[c]
P value[b]	.04[c]	.14	.07	.007[c]	.01[c]
% Protein					
r[a]	0.08	−0.01	−0.02	0.00	−0.14
P value[b]	.89	.75	.75	.99	.93
% Sugars					
r[a]	0.03	0.10	−0.09	−0.27	0.08
P value[b]	.89	.67	.69	.24	.71
Cholesterol (mg/kg)					
r[a]	0.44[c]	−0.49[c]	−0.55[c]	0.58[c]	−0.44[c]
P value[b]	.04[c]	.02[c]	.01[c]	.007[c]	.05[c]
Iron (mg/kg)					
r[a]	0.52[c]	−0.47[c]	−0.50[c]	0.28	−0.35
P value[b]	.01[c]	.03[c]	.02[c]	.22	.12
Magnesium (mg/kg)					
r[a]	0.45[c]	−0.43	−0.39	0.46[c]	−0.38
P value[b]	.04[c]	.05	.08	.03[c]	.09
Folate (μg/kg)					
r[a]	0.57[c]	−0.68[c]	−0.62[c]	0.45[c]	−0.49[c]
P value[b]	.007[c]	<.001[c]	.003[c]	.04[c]	.02[c]

Abbreviations: 6MWT, 6-Minute Walk Test; MSWS-12, 12-item Multiple Sclerosis Walking Scale; TUG, Timed Up and Go test; T25FW, Timed 25-Foot Walk test.
[a]Spearman correlation coefficient score.
[b]Two-sided P value, $\alpha < .05$ was considered significant.
[c]Statistically significant.

shift toward diets lower in fat to diets higher in carbohydrates. The macronutrient proportion of the current US diet consists of 50% carbohydrates, 30% to 35% fats, and 15% to 20% proteins. However, the shift away from fat in the US diet did not result in improved health; instead, the United States has seen a rise in metabolic syndrome, obesity, and diabetes.[33] Obesity is a chronic inflammatory condition that impairs insulin sensitivity, immune function, and metabolic function, and has the potential to lead to immune modulated diseases such as MS.[34] Recent prospective studies have shown that childhood obesity, specifically in females, is a risk factor to the development of MS.[35] In post hoc analysis of the present sample, the higher EDSS score group (5.0-6.0) had a macronutrient proportion that most resembled the current US diet, and the lower EDSS score group had a higher proportion of fats. A recent publication of a large prospective study concluded that a more moderate proportion of calories coming from fats (35%) was associated with a lower risk of death compared with lower intakes. Conversely, diets higher in carbohydrates (>60%) correlated to higher mortality rates.[36]

Diets low in fats and high in carbohydrates could contribute to the documented impairment of lipid and glucose metabolism in MS.[37,38] The increase in carbohydrates in the US diet resulted in increased consumption of refined sugars with higher glycemic responses. The glycemic index indicates the effect that a food has on a person's blood glucose level. Glycemic load refers to the amount of carbohydrate availability in the food multiplied by its glycemic index and is an indicator of both quantity and quality of the carbohydrate consumed.[39] Low glycemic load foods with improved nutrient density such as whole grains and fruits and vegetables have been shown to improve glycemic control and reduce the risk of developing diabetes.[40] Balto et al[13] confirmed that this type of dietary intake was associated with reduced cardiovascular disease symptoms in people with MS. In the presence of high glycemic index foods, the blood glucose level rises too rapidly and the insulin response can be exaggerated and prolonged. This excessive insulin response results in an augmented glucose reduction that triggers an increase in hunger hormone levels, resulting in increased food intake. Over time, this pattern of excessive insulin release, extreme fluctuations in blood glucose levels, and subsequent hunger response leads to insulin resistance followed by metabolic syndrome and, ultimately, diabetes.[41]

Multiple studies have demonstrated an impaired insulin response during and after an oral glucose tolerance test such that there is a higher prevalence of insulin insensitivity, postprandial hyperinsulinemia, impaired fasting glucose concentrations, and an increased susceptibility to fasting hypoglycemia in MS.[42,43] These changes, seen at both the hormonal and mitochondrial levels, may potentially lead to the overutilization of carbohydrates, even during low-level functional activity. This phenomenon has been demonstrated in MS by the increased utilization of carbohydrates as fuel and a lower utilization of free fatty acids at rest and during exercise compared with controls.[44] Typically, free fatty acids are the preferred fuel source at rest and during submaximal activities because the body has larger amounts of fat storage to draw from for the physical activity.[45] In contrast, when carbohydrates are overused there is a premature depletion of energy resulting in fatigue, a decrease in functional performance, and possibly a reduction in physical activity levels. A diet higher in fat increases the amount of free fatty acids in the blood, encouraging fatty acid oxidation and a reduced insulin response.[46] This may partially explain why the present sample saw improved function with higher fat intake.

The well-documented benefits of fat in the diet give additional support for the findings of this study. Fats provide a good source of energy, are the building blocks of cells including myelin, are essential in the absorption of vitamins, signal satiety, and are precursors to many hormones.[47] Current dietary recommendations[48] are based on a 2000-cal/d diet and suggest consuming approximately 65 g/d from total fat (30%) and 20 g/d or less from saturated fat (<10%). The participants in the present study had higher intake of total fat (36%) and saturated fat (11%-12%) than the recommendations. The higher fat intake also indicates an increase in monounsaturated fatty acids and PUFAs. The Mediterranean diet, high in monounsaturated fatty acids, has been shown to be protective in the odds of developing MS,[49] and protective effects of PUFAs have been extensively studied in MS.[32] Omega-3, a type of PUFA, inhibits the production of proinflammatory cytokines and tumor necrosis factor and suppresses the proliferation of T cells and demyelination. With the changing viewpoints on fat intake, new diets are emerging that incorporate an emphasis on healthy fats (nuts, olive oil, avocados, etc) coming from unprocessed whole food sources.

Recently, the ketogenic diet has gained popularity in people with MS because of the perceived metabolic and hormonal benefits associated with consuming diets high in fats. The ketogenic diet is a high-fat (~75%), low-carbohydrate (~5%) diet designed to shunt metabolites away from the tricarboxylic acid cycle to the liver, where ketone bodies are produced. Ketones are easily transported across the blood-brain barrier, supplying the brain with energy. As a result, the decreased reliance on glucose metabolism helps to reduce oxidative phosphorylation and reactive oxygen species' stress on cells.[50] In addition, preclinical studies demonstrate that ketone bodies have a neuronal protective role. The ketogenic diet has been shown to be beneficial in other neurologic diseases, such as Alzheimer disease, Parkinson disease, and epilepsy. More research is needed in the MS population before similar benefits can be stated; however, the theoretical basis for potential benefit has been established.[51]

Another noteworthy finding from this study was that cholesterol, iron, folate, and magnesium significantly correlated with increased scores on the physical component of the SF-36 and improved function. These specific micronutrients play important roles in immune and nervous system function, and their intake has been reported to be lower than that recommended in people with MS.[52] These correlations were present only when using the FFQ. The FFQ gives a better picture of long-term diet and is better at estimating micronutrient intake that fluctuates significantly day-to-day. Two studies have shown that an increase in cholesterol is associated with disability and lesion formation.[53,54] However, cholesterol has been shown to have interdependence with vitamin D levels in the body and may help to explain our findings in this study.[55] Iron is associated with the transport of oxygen, glucose metabolism, neurotransmitter synthesis, and myelin production.[56] Magnesium regulates energy metabolism, membrane stability, and protein, and DNA synthesis and has been shown to have a neuroprotective effect in the central nervous system.[57] Folate, along with vitamin B_{12}, is a factor in the conversion of homocysteine to methionine, and failure of this conversion results in increased homocysteine levels, oxidative stress, DNA destruction, and mitochondrial dysfunction.[7] These findings are consistent with those of Bitarafan et al,[4] who reported a relationship between self-report fatigue and magnesium and folate consumption. To our knowledge, the present data are the first to associate magnesium and folate consumption with standardized gait outcomes in people with MS.

Limitations of this study must be acknowledged. First, use of a cross-sectional design can provide only correlations and not direct causative findings. Second, participants with lower EDSS scores may have more social interaction with friends and family and at work, which allows for more frequent episodes of dining outside of the house, suggesting better QOL and possibly higher fat consumption. In contrast, participants with higher EDSS scores may be dependent on a caretaker for meal preparation. Third, originally a power analysis was not included because this was a pilot study and there was limited information describing the effects of nutrition on functional performance in MS. Since the completion of this study, we discovered an abstract presented at the European Committee for Treatment and Research in MS (ECTRIMS) investigating the relationship between antioxidant intake using the FFQ and the EDSS score and fatigue. Based on their reported correlation coefficient (r = 0.5-0.7),[58] our sample size would need to be 19 to achieve 80% power using an effect size of 0.6 and an α of 0.05. A sample size of 20 from the present study yields powers of 52% to 97% (r = 0.43-0.68). Fourth, dietary assessment methods have well-known limitations. There was a mean 171-kcal/d difference in the two dietary assessments, with participants reporting higher calorie intakes using the FFQ. This could possibly represent overreporting or underreporting on one of the methods. We used both tools to develop a broader overall picture of the patient's diet. It could be hypothesized that short- and long-term diet can affect fatigue and energy levels and that long-term diet can have more potential to affect function. This may explain why we see stronger correlations of nutrients with function when using the FFQ. Studies suggest that using more than one method, as we have done, may strengthen the conclusions drawn from the data.[59]

In conclusion, the findings of this pilot study highlight the potential impact that diet may have on function, fatigue, and QOL in MS. This study expands the current literature examining nutrition in relation to functional outcome measures. More studies are needed to confirm the role of macronutrient ratios and micronutrient intake on daily function. These future studies could identify an ideal dietary profile that could decrease symptoms in people with MS. □

PRACTICE POINTS

- The findings from this study suggest an improved ambulation status and quality of life in people with MS with a macronutrient ratio that favors increased fat intake and decreased carbohydrate intake.
- Dietary factors may affect function and quality of life and should be assessed in individuals with MS to assist in comprehensive patient management.
- Potential exists for the development of dietary guidelines to improve quality of life and function in people with MS.

Acknowledgments: The authors acknowledge Ann Marie Nowicki and Alyssa Simmon for their expert assistance with diet analysis.

Financial Disclosures: The authors declare no conflicts of interest.

Funding/Support: Financial support was provided by the Mark Diamond Research Fund of the Graduate Student Association at the University at Buffalo, The State University of New York.

References

1. Lassmann H, Bruck W, Lucchinetti CF. The immunopathology of multiple sclerosis: an overview. *Brain Pathol.* 2007;17:210-218.
2. Jelinek GA, De Livera AM, Marck CH, et al. Lifestyle, medication and socio-demographic determinants of mental and physical health-related quality of life in people with multiple sclerosis. *BMC Neurol.* 2016;16:235.
3. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis, part II: noninfectious factors. *Ann Neurol* 2007;61:504-513.
4. Bitarafan S, Harirchian MH, Nafissi S, et al. Dietary intake of nutrients and its correlation with fatigue in multiple sclerosis patients. *Iran J Neurol.* 2014;13:28-32.
5. Bagheri M, Maghsoudi Z, Fayazi S, Elahi N, Tabesh H, Majdinasab N. Several food items and multiple sclerosis: a case-control study in Ahvaz (Iran). *Iran J Nurs Midwifery Res.* 2014;19:659-665.
6. Duan S, Lv Z, Fan X, et al. Vitamin D status and the risk of multiple sclerosis: a systematic review and meta-analysis. *Neurosci Lett.* 2014;570:108-113.
7. Kocer B, Engur S, Ak F, Yilmaz M. Serum vitamin B12, folate, and homocysteine levels and their association with clinical and electrophysiological parameters in multiple sclerosis. *J Clin Neurosci.* 2009;16:399-403.
8. Salzer J, Hallmans G, Nystrom M, Stenlund H, Wadell G, Sundstrom P. Vitamin A and systemic inflammation as protective factors in multiple sclerosis. *Mult Scler.* 2013;19:1046-1051.
9. Maker-Clark G, Patel S. Integrative therapies for multiple sclerosis. *Dis Mon.* 2013;59:290-301.
10. Weinstock-Guttman B, Baier M, Park Y, et al. Low fat dietary intervention with omega-3 fatty acid supplementation in multiple sclerosis patients: prostaglandins, leukotrienes, and essential fatty acids. 2005;73:397-404.
11. Bitarafan S, Saboor-Yaraghi A, Sahraian MA, et al. Effect of vitamin A supplementation on fatigue and depression in multiple sclerosis patients: a double-blind placebo-controlled clinical trial. *Iran J Allergy Asthma Immunol.* 2016;15:13-19.

12. Bethoux F, Bennett S. Evaluating walking in patients with multiple sclerosis: which assessment tools are useful in clinical practice? *Int J MS Care*. 2011;13:4-14.
13. Balto JM, Ensari I, Hubbard EA, Khan N, Barnes JL, Motl RW. Co-occurring risk factors in multiple sclerosis. *Am J Health Behav*. 2017;41:76-83.
14. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33:1444-1452.
15. American Thoracic Society/European Respiratory Society. ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med*. 2002;166:518-624.
16. Goldman MD, Marrie RA, Cohen JA. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. *Mult Scler*. 2008;14:383-390.
17. Rudick RA, Cutter G, Reinold S. The Multiple Sclerosis Functional Composite: a new clinical outcome measure for multiple sclerosis. *Mult Scler*. 2002;8:359-365.
18. Sebastiao E, Sandroff BM, Learmonth YC, Motl RW. Validity of the Timed Up and Go Test as a measure of functional mobility in persons with multiple sclerosis. *Arch Phys Med Rehabil*. 2016;97:1072-1077.
19. Block VA, Pitsch E, Tahir P, Cree BA, Allen DD, Gelfand JM. Remote physical activity monitoring in neurological disease: a systematic review. *PLoS One*. 2016;11:e0154335.
20. Weikert M, Suh Y, Lane A, et al. Accelerometry is associated with walking mobility, not physical activity, in persons with multiple sclerosis. *Med Eng Phys*. 2012;34:590-597.
21. Lemos T, Gallagher D. Current body composition measurement techniques. *Curr Opin Endocrinol Diabetes Obes*. 2017;24:310-314.
22. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ*. 1992;305:160-164.
23. Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). *Neurology*. 2003;60:31-36.
24. Flachenecker P, Kumpfel T, Kallmann B, et al. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. *Mult Scler*. 2002;8:523-526.
25. Block G, Woods M, Potosky A, Clifford C. Validation of a self-administered diet history questionnaire using multiple diet records. *J Clin Epidemiol*. 1990;43:1327-1335.
26. Sirard JR, Forsyth A, Oakes JM, Schmitz KH. Accelerometer test-retest reliability by data processing algorithms: results from the Twin Cities Walking Study. *J Phys Activity Health*. 2011;8:668-674.
27. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. *Med Sci Sports Exerc*. 1998;30:777-781.
28. ActiGraph. *Actisoft Analysis Software 3.2 User's Manual*. Fort Walton Beach, FL: MTI Health Services; 2005.
29. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med*. 1998;158:1384-1387.
30. Colbert LH, Matthews CE, Havighurst TC, Kim K, Schoeller DA. Comparative validity of physical activity measures in older adults. *Med Sci Sports Exerc*. 2011;43:867-876.
31. Swank RL, Goodwin J. Review of MS patient survival on a Swank low saturated fat diet. *Nutrition*. 2003;19:161-162.
32. Farinotti M, Vacchi L, Simi S, Di Pietrantonj C, Brait L, Filippini G. Dietary interventions for multiple sclerosis. *Cochrane Database Syst Rev*. 2012;12:CD004192.
33. Cohen E, Cragg M, deFonseka J, Hite A, Rosenberg M, Zhou B. Statistical review of US macronutrient consumption data, 1965-2011: Americans have been following dietary guidelines, coincident with the rise in obesity. *Nutrition*. 2015;31:727-732.
34. Grundy SM. What is the contribution of obesity to the metabolic syndrome? *Endocrinol Metab Clin North Am*. 2004;33:267-282.
35. Palavra F, Almeida L, Ambrosio AF, Reis F. Obesity and brain inflammation: a focus on multiple sclerosis. *Obes Rev*. 2016;17:211-224.
36. Miller V, Mente A, Dehghan M, et al. Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): a prospective cohort study. *Lancet*. 2017;390:2037-2049.
37. Adibhatla RM, Hatcher JF. Altered lipid metabolism in brain injury and disorders. *Subcell Biochem*. 2008;49:241-268.
38. Mathur D, López-Rodas G, Casanova B, Marti MB. Perturbed glucose metabolism: insights into multiple sclerosis pathogenesis. *Front Neurol*. 2014;5:250.
39. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr*. 2002;76:5-56.
40. Siegel KR, Bullard KM, Imperatore G, et al. Prevalence of major behavioral risk factors for type 2 diabetes. *Diabetes Care*. 2018;41:1032-1039.
41. Jakobsen MU, Dethlefsen C, Joensen AM, et al. Intake of carbohydrates compared with intake of saturated fatty acids and risk of myocardial infarction: importance of the glycemic index. *Am J Clin Nutr*. 2010;91:1764-1768.
42. Penesova A, Vlcek M, Imrich R, et al. Hyperinsulinemia in newly diagnosed patients with multiple sclerosis. *Metab Brain Dis*. 2015;30:895-901.
43. Wens I, Dalgas U, Deckx N, Cools N, Eijnde B. Does multiple sclerosis affect glucose tolerance? *Mult Scler*. 2013;20:1273-1276.
44. Mahler A, Steiniger J, Bock M, et al. Is metabolic flexibility altered in multiple sclerosis patients? *PLoS One*. 2012;7:e43675.
45. Venkatraman JT, Pendergast DR. Effect of dietary intake on immune function in athletes. *Sports Med*. 2002;32:323-337.
46. Stinkens R, Goossens GH, Jocken JW, Blaak EE. Targeting fatty acid metabolism to improve glucose metabolism. *Obes Rev*. 2015;16:715-757.
47. Kalish BT, Fallon EM, Puder M. A tutorial on fatty acid biology. *JPEN J Parenter Enteral Nutr*. 2012;36:380-388.
48. Rouen PA, Wallace BR. The 2015-2020 Dietary Guidelines: overview and implications for nursing practice. *Home healthc Now*. 2017;35:72-82.
49. Sedaghat F, Jessri M, Behrooz M, Mirghotbi M, Rashidkhani B. Mediterranean diet adherence and risk of multiple sclerosis: a case-control study. *Asia Pac J Clin Nutr*. 2016;25:377-384.
50. Sullivan PG, Rippy NA, Dorenbos K, Concepcion RC, Agarwal AK, Rho JM. The ketogenic diet increases mitochondrial uncoupling protein levels and activity. *Ann Neurol*. 2004;55:576-580.
51. Storoni M, Plant GT. The therapeutic potential of the ketogenic diet in treating progressive multiple sclerosis. *Mult Scler Int*. 2015;2015:681289.
52. Ramsaransing GS, Mellema SA, De Keyser J. Dietary patterns in clinical subtypes of multiple sclerosis: an exploratory study. *Nutr J*. 2009;8:36.
53. Weinstock-Guttman B, Zivadinov R, Horakova D, et al. Lipid profiles are associated with lesion formation over 24 months in interferon-beta treated patients following the first demyelinating event. *J Neurol Neurosurg Psychiatry*. 2013;84:1186-1191.
54. Weinstock-Guttman B, Zivadinov R, Mahfooz N, et al. Serum lipid profiles are associated with disability and MRI outcomes in multiple sclerosis. *J Neuroinflammation*. 2011;8:127.
55. Weinstock-Guttman B, Zivadinov R, Ramanathan M. Inter-dependence of vitamin D levels with serum lipid profiles in multiple sclerosis. *J Neurol Sci*. 2011;311:86-91.
56. Piñero DJ, Connor JR. Iron in the brain: an important contributor in normal and diseased states. *Neuroscientist*. 2000;6:435-453.
57. Chang JJ, Mack WJ, Saver JL, Sanossian N. Magnesium: potential roles in neurovascular disease. *Front Neurol*. 2014;5:52.
58. Shaygannejad V, Heidari M, Maljaie MB, Mirmosayyeb O. Relationship between dietary intakes of antioxidant with EDSS and fatigue scale in MS. ECTRIMS Online Library website. https://onlinelibrary.ectrims-congress.eu/ectrims/2016/32nd/145529/marzieh.heidari.relationship.between.dietary.intakes.of.antioxidant.with.edss.html?f=menu=6*ce_id=1031*ot_id=13997*media=2. Published September 14, 2016.
59. Liu K. Statistical issues related to the design of dietary survey methodology for NHANES III. *Vital Health Stat 4*. 1992;27:3-14; discussion 15-23.