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Can a healthy high fat diet improve fatigue symptoms in patients with relapse and remitting multiple sclerosis?

Capstone PA653

Elizabeth Henry and Sarah von Euler

## Abstract

**Objective:** Assess the effects of healthy high-fat diets such as Ketogenic and the Mediterranean diet on fatigue symptoms among patients with relapse and remitting multiple sclerosis (RRMS). **Design:** Systematic literature review **Background:** Multiple sclerosis (MS) is a debilitating autoimmune disease that affects a person's central nervous system with one of the most common complaints being fatigue reported in about 80% of patients.<sup>1</sup> Unfortunately, MS is not curative, resulting in a plethora of hypotheses trying to improve symptoms like fatigue. One of the ideas is consuming a healthy high-fat diet compared to the standard American diet would improve fatigue-like symptoms. **Methods:** Google Scholar was searched using the terms "multiple sclerosis, high-fat diets, fatigue, and "trial" RRMS." Articles on Google Scholar were filtered based on study design, randomized control trials and observational studies, human subjects, healthy high-fat diets, and an outcome of fatigue resulting in 3 articles. **Results:** There was limited significant data found among the three studies making recommendations to eat a healthy high-fat diet difficult. **Conclusion:** Based on the results high-fat diets appear to be safe and tolerable for patients, however, current research has failed to demonstrate a significant improvement in fatigue.

## Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating disease that affects approximately 2.8 million people worldwide<sup>2</sup>. Multiple sclerosis can be subcategorized into four different types based on clinical presentation. These categories include clinically isolated syndrome, relapse and remitting, primary progressive, and secondary progressive. Among the four subtypes, relapse and remitting multiple sclerosis (RRMS) is the most common affecting about 85% of patients<sup>3</sup>. These patients' experiences are highly variable with many different clinical presentations, and rates of progression. RRMS is characterized by a relapsing phase with significant symptoms followed by a period of remission, either to baseline or to a less severe level of symptoms. During this period of remission patients do not progress in their disease state; however, new symptoms may appear during a relapse period. RRMS often leads to secondary progressive MS. Progression to secondary progressive MS is diagnosed when a patient experiences sequential attacks without returning to baseline. MS symptoms can manifest in many ways such as dysesthesia, gait disturbances, fatigue, spasticity, cognitive changes, etc. Fatigue is the most common complaint reported in about 80% of patients<sup>1</sup>. Again, each patient's symptoms are unique to the individual as it depends on the location of the brain that has been destroyed by beta-amyloid plaques<sup>1</sup>.

This debilitating disorder is still quite puzzling to scientists which limits the treatment options for patients. There is currently no curative treatment, instead, current pharmacologic treatments aim to slow disease progression rather than cure the disease or treat individual symptoms. For many patients, current pharmacologic treatment options provide insufficient control of MS progression and symptom outcomes.<sup>4</sup> Due to this significant gap in treatment, dietary modification has been explored as a potential adjuvant therapy to disease-modifying medications<sup>4</sup>. Many diets have been investigated and have various proposed mechanisms for

combating symptoms. Diets such as the Mediterranean diet have been studied previously as a possible intervention. These studies have found that individuals who adhere to the Mediterranean diet have a lower risk of developing many chronic diseases, including multiple sclerosis.<sup>5</sup>

The proposed mechanism behind this observed benefit is the high antioxidant capacity of the Mediterranean diet and the omega-3-induced inhibitory reaction on the Nuclear Factor kB pathway.<sup>5</sup> Relapses in RRMS typically result from systemic inflammation which leads to cerebral inflammation and thereby the formation of new beta amyloid lesions on the brain, so preventing inflammation with a high polyunsaturated diet could be beneficial to RRMS patients. Immunologic therapy aims to reduce inflammation both with immunotherapy and corticosteroids, however, it is known that diet can contribute to inflammation.<sup>6</sup> Two transcription factors have been found to link inflammation with autoimmunity. These factors are nuclear transcription factor- kB (NF-kB) and activator protein (AP-1).<sup>6</sup> Both NF-kB and AP-1 are activated in MS and have been found to induce the expression of several proinflammatory molecules leading to the neurologic symptoms and lesion formation characteristic of MS.<sup>6</sup> NF-kB can be activated by viruses, cytokines, and oxidative stress, along with dietary components such as saturated fats and trans-fats.<sup>6</sup> The Mediterranean diet aims to reduce oxidative stress with foods rich in antioxidants and reduce saturated and trans fats by replacing them with polyunsaturated fats such as Omega-3s found in fish oils and olive oils.<sup>6</sup>

While preliminary research proposes a promising hypothesis for dietary management of MS symptoms and progression, clinical trials focusing on the outcomes of strict adherence to these dietary modifications have only just begun in recent years. Our aim in this study is to examine whether there is a significant improvement in RRMS-related fatigue in patients who adhere to diets that are high in polyunsaturated fats and low in trans fats and saturated fats.

## Case

LJ is a 32 y/o woman who was diagnosed with relapsing and remitting multiple sclerosis 9 years ago and presents to the clinic for worsening fatigue symptoms, which is making it hard for her to get through her workday. She has been stable on pharmacotherapy besides her fatigue which is now persisting even during periods of remission. Her friend recently started a diet high in polyunsaturated fats to help reduce her overall inflammation. The friend saw in her research that high polyunsaturated fat diets can help with fatigue symptoms related to inflammation in RRMS patients. LJ wants your medical expertise and advice as to if this would be a good adjunct to her therapy.

## Clinical question

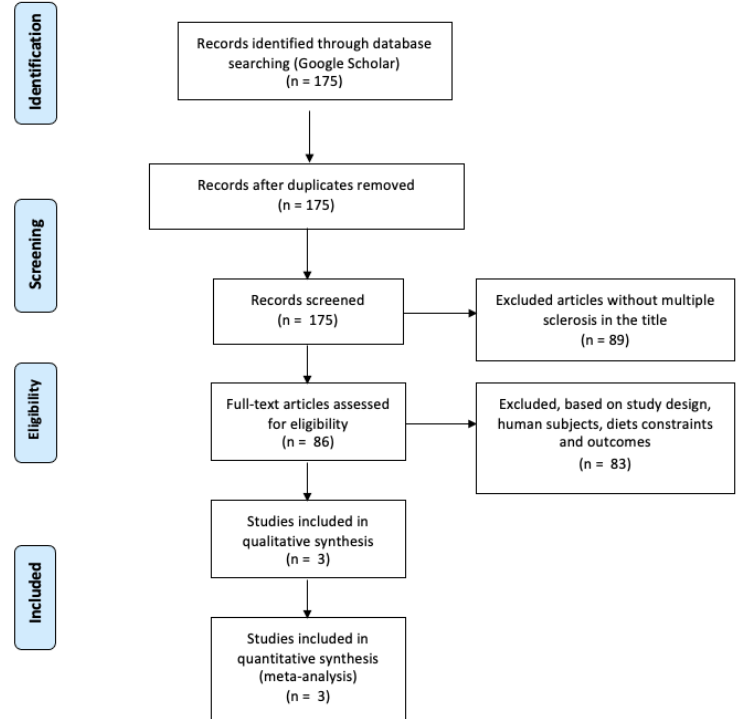
Among patients with relapsing and remitting multiple sclerosis, would patients adhering to a healthy high-fat diet, such as the Mediterranean diet, see a significant improvement in fatigue when compared to patients eating a standard American diet?

## Methods

In September 2022, Google Scholar was searched using the terms “multiple sclerosis, high-fat diet, fatigue, “trial,” and “RRMS.” One hundred seventy-five results were populated with duplicates removed. All 175 articles were screened for “multiple sclerosis” in the opening title, which excluded 89 articles from this search. While initially hoping to find exclusively randomized control trials, we included one single arm observational clinical trial in our final analysis due to similarities in metrics with the two initial randomized control trials found.

Further screening on the remaining 86 articles was completed based on study design, including only randomized control trials and observational studies, human subjects, healthy high-fat diets, and an outcome of fatigue. This narrowed down the included articles to 3 studies which were then selected

as the ones for quantitative synthesis, including the one stated above. Our three studies were selected based on similarities in the proposed diets, as well as similarities in the metrics used to assess our desired end point which was reduced fatigue over the course of the intervention.



## Results

Study 1: Phase II study of ketogenic diets in relapsing multiple sclerosis: safety, tolerability and potential clinical benefits <sup>7</sup>

Study objective: To assess the tolerability and safety of a ketogenic diet in patients with relapse and remitting MS and determine the impact strict nutritional parameters have on clinical and laboratory outcomes.

### Study design

This study is composed of 65 patients with RRMS defined by the McDonald criteria who range in age from 12-55. Inclusion and exclusion criteria are included in table 1 below. The study population had a mean age of 40 with 55 females and 9 males. Of the patients enrolled 20 were overweight at baseline, 40 were obese and 4 were within the normal range by BMI classification. The average disease duration was 8.4 years. The time since the last relapse was 4.4 years on average, and the average baseline Expanded Disability Status Scale (EDSS) was

2.3 with a range from 1-6 among study participants. All but one patient was currently taking disease-modifying therapy with the most common being Natalizumab (24 patients) and Fingolimod (14 patients) and the average time on current therapy was 24 months. Forty one of the 64 patients in the study population had previously tried another diet as a method for symptom management, however, patients were excluded if they had previously adhered to a ketogenic diet (KD).

Table 1. Patient Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
<p>Demonstrated stability in their disease state with their current therapeutic regimen</p> <p>Disability score of <math>\leq 6</math> determined by the expanded disability status scale (EDSS)</p> <p>Patients with hypercholesterolemia and nephrolithiasis required explicit written permission from their physician to enroll</p>	<p>Patients who had experienced progression in the last 6 months</p> <p>Pregnant or planning to become pregnant</p> <p>Underweight or had a diagnosis of an eating disorder</p> <p>Changed disease-modifying treatment during the study period</p> <p>Previous adherence to a ketogenic diet</p>

The sample size for the study was determined through a priori sample size calculations. The study was determined to have 80% power with a paired T-test with a two-sided significance level of 5% with a mean change in modified fatigue impact of 5.6 points.

Study subjects participated in a baseline visit before beginning the diet intervention and 3 visits throughout the study while they were adhering to the diet at months 1,3 and 6. At the initial visit, subjects met with the study dietician who provided guidance and education on the modified ketogenic diet. The modified ketogenic diet explored in this study required patients to restrict net carbohydrates to <20 g/day and to increase their intake of healthy fats. In addition, subjects were instructed to begin a multivitamin and were assessed for calcium deficiency frequently. If they were found to be deficient in calcium participants were instructed to begin calcium supplementation. The dietician followed up with patients at week 2 to provide guidance and encouragement for diet adherence. EDSS scores were determined at each visit along with MS functional composite testing at baseline and 6 months. Patients also recorded perceived outcomes, which included depression screening using Beck's depression inventory and fatigue assessment using the modified fatigue impact scale. These endpoints were assessed at baseline, 3 months, and 6 months. The MS fatigue severity scale and MS quality of life-54 were added after the first 20 patients were enrolled and therefore, data was only available for the final 45 patients.

Adherence to the diet was monitored using daily urine ketone strips which were photographed and sent in to the research team daily. A negative ketone strip or a strip without the date labeled was marked as non-compliant. A subject was considered to be compliant with the study if they adhered to the diet for more than 85 days.

The data from this study was analyzed using an intention-to-treat approach. Research was analyzed without inputting any data points for missing data. Data from all subjects who completed the 3-month and 6-month visits were included.

### Study results

Seventy seven patients were screened for eligibility and 65 patients were enrolled. One patient was enrolled and never began the diet due to a change in life circumstances. Of the 65 patients enrolled in the study, 53 were considered KD compliant. Of the 11 patients who were categorized as non-compliant, 5 were lost to follow-up, 3 were noncompliant with KD, 2 withdrew from dietary side effects, and 1 withdrew due to a new diagnosis of Crohn's disease. The diet was found to be tolerable to the majority of study participants. Of the patients who were adherent to the diet, 43% experienced constipation and 18% had diarrhea which were the two most frequently cited complaints. The secondary endpoint, fatigue ratings were provided by patients and were analyzed using an intention-to-treat analysis before and after their diet. The mean change from baseline in the modified fatigue impact score showed a mean changed from baseline of  $-14.4 \mp 14.9$  points at 6 months with a p value of  $< 0.001$ . The mean change in fatigue severity at 6 months was  $-3.4 \mp 5.8$  with a p value of 0.002. Both of these have a confidence interval which crosses 0 which indicates that the research is not sufficient to determine whether there is an association between fatigue and the KD diet.

### Study critique

The original intention of this paper was to demonstrate the safety and tolerance of the ketogenic diet in patients with MS. Researchers later decided they would investigate the impact of the ketogenic diet on symptoms such as fatigue, depression and quality of life. This meant the sample size and statistical power of the study was not designed to show the efficacy of the KD diet on reduction of symptoms. In order to properly determine whether the KD diet would be efficacious in symptom reduction, a randomized control trial with a larger sample would be required. Understanding the challenges to create a blinded study for a complicated diet regimen makes a randomized control trial design almost impossible. The data provided in this study indicate that further research is likely to find significant improvement in many of the metrics explored in this study, however, the current study did not have the statistical power to demonstrate whether there was a significant reduction in fatigue associated with adherence to a ketogenic diet. The mean change indicates that there is a possibility that in a larger randomized control trial, a significant outcome may be found and that outliers, non adherence, and small sample size may be skewing data. The study was limited by the lack of a matched control group on a "regular diet", citing cost, planning, and challenges with recruitment as the major barriers.

## Study 2: Potential of modified Mediterranean diet to improve quality of life and fatigue severity in multiple sclerosis patients: a single-center randomized control trial<sup>5</sup>

### Study Objective

To investigate the effects of a modified Mediterranean diet on the quality of life and severity of fatigue amongst patients with relapse and remitting multiple sclerosis.

### Study design

This was a 6-month, single-center, single-blinded randomized control trial of 180 participants with relapsing and remitting multiple sclerosis recruited in Isfahan, Iran. The inclusion and exclusion criteria are found below in Table 2. Those 180 people were then randomly assigned to either a modified Mediterranean intervention (n=90) or the traditional Iranian diet (n=90) via a computer generator stratified by age and sex.

Table 2. Patient Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
RRMS cases with EDSS up to 3 Writing ability and memory strength Age between 20-60 y/o Received dimethyl fumarate 240 mg BID in the last year	Patient with viral infections like Epstein Barr Patients with other forms of MS Disease duration of less than 1 year consuming special food supplements or fatigue modifying drugs Allergies and other autoimmune diseases >40% of the food questionnaire was left blank Major medical illness Current smoker High intake of corticosteroids Participants in other trials

The modified Mediterranean group was monitored and adjusted by an expert dietitian to ensure the consumption of higher amounts of fruits, vegetables, whole grains, monounsaturated fatty acids, fish, and minimal consumption of dairy, meats, and poultry. In the control group, the traditional Iranian diet consisted of 12% protein, 58% carbs, and 30% fat. They were limited to low-fat dairy products, whole grains and were advised to increase their red meat, solid oils, refined grains, and moderately intake legumes, fruits, and vegetables. Adherence to each group's diet was monitored weekly by phone calls and monthly face-to-face interviews. A 168-item question was completed every 2 months; nutrition software was utilized to determine each participant's intake of dietary nutrients.

At the beginning of the study, participants completed a demographic, MS quality of life 54-item questionnaire. The questions encompassed 12 different subcategories that were then organized into 2 summary categories: physical and mental health. Based on the answers to the 54



questions a score ranging from 0-100 was calculated to make up both the physical and mental health composite scores. A high score corresponded to a better quality of life.

Fatigue was defined as a lack of physical or mental energy and was subclassified into chronic and acute. Chronic fatigue was quantified by the fatigue severity scale which was a 9-item questionnaire with scores ranging from 9-63. The higher the score the more fatigue the participant felt. Acute fatigue was assessed using the analog fatigue scale, which ranged from 0-10, the lower the number the more fatigue the participant experienced. All the data were normally distributed using the Kolmogorov-Smirnov test. Mann-Whitney compared the data between the modified Mediterranean and the traditional Iranian diet. A multivariate analysis of covariance was used to adjust for age, gender, family history, duration of MS, and education level among the 2 groups.

### Study results

This study included 180 participants who were randomized into a control diet which was the standard Iranian diet, and a study group who adhered to a modified Mediterranean diet. Patients who adhered to the modified Mediterranean diet did not report any statistically significant improvement in acute fatigue when compared with the control diet. The mean difference in acute fatigue was found to be  $0.2 \pm 2.0$  vs  $0.1 \pm 0.8$  with a p value of 0.184. The mean difference for chronic fatigue, however, was found to be significant between the two groups after performing significant stratification and adjusting for age, gender, education, family history, and duration of MS symptoms. Researchers found that there was a  $9.8 \pm 11.5$  decrease in chronic fatigue severity for modified Mediterranean diet with a p value of 0.001 compared to the control group which showed mean change from baseline of  $0.3 \pm 4.3$  with a p value of 0.562 after a 6 month follow up. The change from baseline in chronic fatigue, while statistically significant, has a confidence interval which crosses 0 which means it is not possible to make an assertion that the modified Mediterranean diet can significantly improve fatigue.

### Study critique

This study provides limited insight into the therapeutic ability of the modified Mediterranean diet in addressing chronic fatigue experienced by many patients with RRMS. The researchers were unable to perform a double-blinded or triple-blinded study due to the nature of the intervention being proposed. It would not be possible for the participants to be unaware of their assigned treatment group. In addition, researchers faced challenges in assessing adherence to the diet and assert that patients may not have accurately reported food consumption due to differences in social class. The study showed that many patients who adhered to the modified Mediterranean diet experienced a reduction in fatigue, however, researchers were unable to quantify how much the modified Mediterranean diet improved quality of life and fatigue. The authors suggest further research to assess the efficacy of the diet with a larger sample size and a longer intervention in order to eliminate the effect of variability among study participants and

better evaluate the effects of the modified Mediterranean diet in a broader population of patients with RRMS.

Study 3: A randomized controlled trial investigating the effects of a Mediterranean like diet in patients with multiple sclerosis associated cognitive impairments and fatigue<sup>8</sup>

#### Study objective

To identify the effects of a Mediterranean-like diet compared to a nutritionist-aided standard diet on fatigue over a years time.

#### Study design

This single-blinded randomized control trial recruited 115 patients with RRMS from Sina University Hospital in Tehran to study for 1 year. After assessment based on inclusion and exclusion criteria which are listed in Table 3 below, 80 subjects were selected for the study. The inclusion and exclusion criteria were established to limit bias during the interpretation of results.

Table 3. Patient Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
RRMS status defined by McDonald 2010 MS diagnostic criteria In a remitting phase with no relapse in the past 3 months Undergoing beta interferon treatment Expanded disability score <5.5 Age 18-55 Body mass index 18-30 kg/m <sup>2</sup>	Changes in disease-modifying therapy Use of cytotoxic, antipsychotic and cortisone medications History of drug abuse Other neurological conditions besides MS Psychological or chronic disorders Pregnant, planning to become pregnant or breastfeeding

The 80 patients were randomly divided evenly into 2 groups: a Mediterranean-like diet group and a standard healthy American diet using a block method. The modification to the Mediterranean-like diet was the removal of wine and some other unspecified items. The standard diet was nutritionist guided and based on the United States Department of Agriculture. An initial history and physical including a neurological exam utilizing the Kurtzke expanded disability status scale (EDSS) and 25-foot walk test was completed. Age, sex, education level, job, and BMI were all collected as a baseline. A fatigue assessment was done with the modified fatigue impact scale (MFIS) as well as a baseline cognitive assessment using minimal assessment of cognitive function in the MS questionnaire. The MFIS is a 21-item questionnaire

that encompasses physical, cognitive, and psychosocial function status. Patients initially met with a registered dietitian to discuss their dietary interventions, then attended monthly meetings to modify macronutrients if their weight fluctuated. Adherence to the dietary intervention was measured using a 6-item questionnaire every 12 weeks.

The Kolmogorov-Smirnov test was used to assess the normality of data, where Chi-squared was applied to categorical specifics. Comparisons between the 2 groups were determined by the Mann-Whitney U test and analysis of covariance (ANCOVA) test, which took into account diet adherence scores, age, BMI, and baseline values. A p-value <0.05 was considered significant.

### Study results

At the end of the study 8 participants were lost to follow up, 6 from the Mediterranean-like group and 2 from the standard healthy diet group. The MFIS scores at baseline were significantly higher among the randomly selected Mediterranean-like diet group compared to the standard diet group. After a year of dietary interventions, the MFIS scores significantly decreased within both groups. After adjusting for age, changes in Mediterranean diet adherence scores, BMI changes, and fatigue scores at baseline using ANCOVA, a more significant decrease in the Mediterranean-like diet was seen. Specific values can be found in table 4.

In order to compare data points between our three studies, a mean difference was calculated. A difference of -4.7 points was found in the intervention group, and a difference of -0.71 was found in the control group when comparing fatigue before intervention and fatigue after intervention. This data was not reported in the original paper, however, so it is not reflected in table 4.

Table 4. Modified Fatigue Impact Scale Scores between Modified Mediterranean like Diet vs Standard Diet

Variable	Modified Mediterranean like diet intervention (n=34)	Standard diet intervention (n=38)
Fatigue score at baseline	40.05 ± 4.22	38.19 ± 4.01
Fatigue score after intervention	35.30 ± 4.20	37.48 ± 4.36
P value	0.040	0.030

### Study critique

A strength of the study was the design method: a randomized control trial, but the small sample size limits the validity. The 6-question adherence protocol could be interrupted as a weakness. This method allows for participants to be subjective, though diet adherence was accounted for using ANCOVA. All patients in the study were undergoing beta interferon treatment, which removes bias when interpreting results. Though, dietary supplements were not recorded in this study that should be included or excluded from data in future studies to ensure supplements are not interfering with results. It was mentioned that MS patients with higher BMI tend to

experience more fatigue. Both groups' BMI was significantly reduced which could be an attenuating factor. Lastly, a longer study could be beneficial in the effectiveness of the Mediterranean-like diet in protecting against fatigue symptoms. Following up with these individuals years later to see if they continued the Mediterranean-like diet and if their fatigue symptoms continued to decline could improve the quality of this research.

## Discussion

Table 5. Overview of studies

	Brenton et al	Moravejolahkami et al	Razeghi-Jahromi et al
Design	Single-arm observational study	Single-center randomized control trial	Single-center, single- blinded randomized control trial
Sample	n=65	Intervention: n=90 Control: n= 90	Intervention: n=40 Control: n=40
Population/Setting	Setting: UVA, Charlottesville, VA	Setting: Isfahan, Iran All patients recruited had previously adhered to a traditional Iranian diet	Setting: Sina University Hospital in Tehran, Iran
Gender	M - 13% F - 87%	M - 17% F - 83%	M - 20% F - 80%
Primary Endpoint	Safety and Tolerability of a Ketogenic Diet	MS quality of life: 54 item questionnaire Fatigue: fatigue severity scale 9-item questionnaire	Fatigue: Modified fatigue impact scale (MFIS) 21- item questionnaire
Fatigue	MS Fatigue Severity Score (MSFSS) Modified Fatigue Impact Scale (MFIS)	Fatigue severity scale 9-item questionnaire	Modified fatigue impact scale (MFIS) 21- item questionnaire
Adherence	Positive, ketone strip with the date sent to research team daily Adherence to diet for >85 days	Weekly phone calls Monthly face-to-face interviews 168-item question every 2 months nutrition software to determine participant's intake of dietary nutrients	6-item questionnaire done every 12 weeks

Results	Mean change from baseline in MFIS = -14.4 ± 14.9 points at 6 months. P value=< 0.001 Mean change MSFSS at 6 months = -3.4 ± 5.8. p value = 0.002.	Mean Change from baseline with modified Mediterranean Diet: 9.8 ± 11.5 P value = 0.001  Mean Change From Baseline with Standard Diet: 0.3 ± 4.3 P value = 0.562	Fatigue score post intervention with Mediterranean-like diet: 35.30 ± 4.20 P value = 0.04  Fatigue score post intervention with standard diet: 37.48 ± 4.36 P value = 0.03
Application	There was no significant improvement in the mean change of MSFSS or MFIS scores.	No significance in acute or chronic fatigue in patients that adhered to the modified Mediterranean diet	Significant ↓ in fatigue symptoms among the modified Mediterranean-like diet group

A diet high in polyunsaturated fats has been proposed as a potential symptomatic treatment for patients with relapsing and remitting multiple sclerosis, however, current research has been unable to demonstrate a significant reduction in fatigue among patients adopting a high-fat diet. Relapse and remitting multiple sclerosis is a progressive degenerative disease with no curative treatment.<sup>3</sup> While a definitive treatment is an ultimate goal, supportive treatments are the current therapies for patients. A high-fat diet has been proposed as a potential adjunctive therapy to traditional biologic treatment with proposed benefits for many of the symptoms associated with multiple sclerosis.<sup>4</sup> The results of our literature review provide evidence that a healthy high-fat diet is tolerable and safe for patients undergoing chronic treatment with biological medications for RRMS. The proposed mechanism for the improvement in symptoms is largely related to the anti-inflammatory properties of polyunsaturated fats, proposing that many of the symptoms experienced by patients living with MS are due to inflammation in the nervous system.<sup>6</sup> Among RRMS symptoms, fatigue has been the most widely researched. The three studies above explored the impact of a healthy high fat diet on fatigue. Each of the studies examined fatigue using a scaling system that used self reported patient ratings to assess the impact of fatigue on each patient's daily life before, during, and at the end of the study.

Brenton et al. measured fatigue using the modified fatigue impact score as well as the multiple sclerosis fatigue severity scale.<sup>7</sup> The modified fatigue impact scale asks patients a series of 21 questions that fall into physical, cognitive, and psychosocial categories to assess the impact that fatigue had on a patient's daily life. Scores ranged from 0-84 or were analyzed based on a specific subcategory of interest.<sup>9</sup> The Multiple Sclerosis Fatigue Severity Scale is an abbreviated 9-question survey that rates fatigue on a scale from 9-63.<sup>10</sup> Patients in this study were instructed to follow a modified ketogenic diet which encouraged the consumption of polyunsaturated fats.<sup>7</sup> Fatigue ratings were analyzed using an intention-to-treat analysis. The

mean change from baseline in the modified fatigue impact score showed a mean change from baseline of  $-14.4 \mp 14.9$  points at 6 months with a p value of  $< 0.001$ .<sup>7</sup> The mean change in fatigue severity at 6 months was  $-3.4 \mp 5.8$  with a p value of  $0.002$ .<sup>7</sup> Both of these have a confidence interval which crosses 0 which indicates that the research is not sufficient to determine whether there is an association between fatigue and the KD diet. This study was an observational single arm cohort study which meant that researchers were unable to compare the observed change in fatigue scores to a control population. In addition, 11 patients did not complete the diet as it had been prescribed, and therefore were carried forward with intention to treat analysis. The study design as well as the small sample size and loss of patients to follow up impedes our ability to draw conclusions about the effectiveness of the proposed dietary intervention on patients with RRMS.

Moravejolahkami et al focused on the overall quality of life of their patients with a secondary outcome of fatigue.<sup>5</sup> They sub categorized fatigue into acute and chronic which was measured with a fatigue severity scale that consisted of a 9-item questionnaire. When examining the results, researchers found that there was not a significant improvement in acute fatigue, however, over time, they noticed an improvement in chronic fatigue. Analysis found a  $9.8 \mp 11.5$  decrease in chronic fatigue severity for the intervention group adhering to a modified Mediterranean diet compared to the control group who showed mean change from baseline of  $0.3 \mp 4.3$  with a p value of  $0.562$  after a 6 month follow up.<sup>5</sup> The change from baseline in chronic fatigue among patients in the intervention group, while statistically significant, has a confidence interval which crosses 0 which means it is not possible to make an assertion that the modified Mediterranean diet can significantly improve fatigue.

This study provided the largest sample size, with intervention and control groups of 90 patients each.<sup>5</sup> The increased sample size, however, is still relatively small which may account for the wide confidence interval which renders inconclusive results. Additionally, this study, along with the study by Razeghi- Jahromi et al, took place in Iran with patients who adhered to a traditional Iranian diet prior to initiating the study.<sup>5,8</sup> This limits our ability to apply the results of this study to the case patient. The American diet is high in trans fats and saturated fats which have a negative impact on inflammation and therefore, it is challenging to compare the differences observed between the intervention and control groups in this study to a control group that is based on the standard American diet.

Razeghi-Jahromi et al used the modified fatigue impact scale (MFIS) revealing the most significant impact of the Mediterranean-like diet on fatigue compared to Moravejolahkami et al and Brenton et al.<sup>8</sup> Though this study was the strongest amongst the three there were still many improvements discussed above that would enhance the validity of their data. This study found that the patients in the intervention group saw a change in fatigue scores from  $40.05 \pm 4.22$  at

baseline to  $35.30 \pm 4.20$  after the intervention.<sup>8</sup> The control group, which remained on a standard Iranian diet, saw a change in fatigue scores from  $38.19 \pm 4.01$  at baseline to  $37.48 \pm 4.36$  at the end of the observation period with a P-value of 0.030.<sup>8</sup> The research found that at the end of the observation period, the intervention group had a significantly lower fatigue score than the control group of  $35.30 \pm 4.20$  v  $37.48 \pm 4.36$  with a P-value of 0.040.<sup>8</sup> This indicates that there was a greater reduction in fatigue among the patients on the Mediterranean-like diet when compared with the controls. This study did not report the mean difference in fatigue scores and rather focused on the comparison between the intervention and control groups in order to assert that their findings were significant. We calculated a mean difference after completing our literature and found a difference of -4.7 points was found in the intervention group, and a difference of -0.71 was found in the control group when comparing fatigue before intervention and fatigue after intervention.

Razeghi-Jahromi et al study was completed in Iran with all participants of the Muslim culture. It was mentioned that modifications were made to the Mediterranean-like diet to follow the Muslim culture. This makes the comparison to the case patient challenging because of unknown cultural differences. It was this study that fueled the recommendation made towards the case patient though further investigation is warranted.

### Application to patient

According to this research, eating a diet high in healthy fats, such as polyunsaturated fats, does not seem to have a significant impact on fatigue in patients with RRMS. With that being said it would not be unreasonable for LJ to try a diet similar to the ones studied, since she has not found anything to help relieve her symptoms. Certainly, this lifestyle modification could be beneficial and she has no risk in giving these diets a try. A diet high in healthy fats like the Mediterranean diet or ketogenic diet would be recommended to LJ.

### Conclusion

Based on the results of our research high-fat diets appear to be safe and tolerable for patients, however, current research has failed to demonstrate a significant improvement in fatigue. The majority of available research is preliminary studies with relatively small sample sizes and limited study designs indicating that with additional research, a significant association between dietary intervention and fatigue may be found. Studies with close follow-up, larger sample sizes, and better objective comparison between study and control groups are necessary prior to asserting a high-fat diet as an efficacious adjunctive treatment of fatigue in relapse and remitting multiple sclerosis.

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