Original article

ADAPTED MEDITERRANEAN DIET IMPACT ON THE SYMPTOMS OF CHRONIC FATIGUE, SERUM LEVELS OF OMEGA-3 POLYUNSATURATED FATTY ACIDS (PUFAS) AND INTERLEUKIN 17 (IL-17) IN PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS UNDERGOING DISEASE-MODIFYING THERAPY: A PILOT STUDY

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SUMMARY

Purpose: This pilot study was designed to investigate the impact of a moderate-calorie Mediterranean diet compared to a regular diet with omega-3 PUFAs (eicosapentaenoic and docosahexaenoic acids) supplementation on fatigue symptoms in patients with relapsing-remitting multiple sclerosis (RRMS) and to assess the optional benefit of the diet on their quality of life.

Material/Methods: This 12-month pilot study was conducted in 2021 at the Department of Neurology, Medical University – Pleven, Bulgaria. A total of 60 patients with RRMS aged 18-64 were selected from the database of the Neurology Clinic at the University Hospital “Dr Georgi Stranski” – Pleven. From the selected patients, only 30 were included in the pilot phase and respectively assigned to the nutritional arms. Blood samples were collected twice – at the first and second visit in 3 months, for metabolic and dietary parameters analysis. Symptoms of fatigue were assessed with Fatigue Scale for Motor and Cognitive Functions (FSMC) and Modified Fatigue Impact Scale (MFIS).

Results: From the 30 participants included in the study, 17 patients attended the clinic centre for complete follow-up; the remaining 13 were only partially observed. The dynamics of the followed-up parameters showed a statistically significant change in the body mass index (BMI), the fatigue symptoms in the FSMC and MFIS scales, total cholesterol and triglycerides levels, and the serum concentrations of IL17A, EPA and DHA. The metabolic caloric values were also found to be significantly changed.

Conclusions: Despite the small study size limitation, this pilot study might be of benefit for further extensive research on the potential favorable impact of diet and lifestyle modifications on the symptoms of fatigue in multiple sclerosis patients.

Keywords: relapsing-remitting multiple sclerosis, Mediterranean diet, chronic fatigue, polyunsaturated fatty acids.

INTRODUCTION:

Multiple sclerosis (MS) is a chronic, autoimmune, demyelinating and neurodegenerative disease of the central nervous system (CNS) with female predominance and usual debut in the third or fourth decade of life. The molecular and tissue manifestation of systemic inflammation and varying degree of autoimmune process activation...
leads to demyelination of the white matter. This demyelination can be with the presence or absence of plaques, gliosis and axonal damage resulting in impaired central neuronal conduction and symptoms of neurological deficit. [7] Approximately 15% of patients have a primary progressive form of the disease; 40% may develop secondary progressive MS with relapsing-remitting phases later in time. [2] For the period 1990-2016, the reported incidence of MS in Bulgaria has increased by 20.1%, which brings us closer in incidence to countries such as Belgium, Germany, Estonia, Malta, Switzerland, Hungary and some countries in the Middle East. [3] Symptoms vary greatly between individuals, and their severity or progression is generally unpredictable. Complex environmental and endogenous factors contribute to the genesis of MS. [4, 5, 6] Researchers have positively concluded the interplay between age, sex, genetic predisposition, bacterial or viral infections, sunlight and seasonal rhythms, physical activity and stressful life events on the MS clinical presentation. Translational studies are ongoing to determine the role of new factors such as the human microbiome, nutrigenomics and nutrition, proteomics and metabolomics, and evaluate their potential impact on the disease severity and progression. [7, 8, 12-15] Multiple innovative treatment strategies, including newer disease-modifying therapy and modern neurosurgical techniques like stereotactic surgery, minimally invasive CNS surgery with navigation and deep brain stimulation, have been explored for the management of general symptoms and detected CNS lesions. [9-11]

Recently, randomized controlled trials investigating the effects of plant-based and omega-3 supplemented low-fat diets in MS have reported favorable outcomes on fatigue among patients with RRMS. Published data is optimistic, but the evidence is still insufficient for definitive conclusions. [16-21]

**Study focus:** The present study focuses on the nutritional effects of an adapted Mediterranean diet on fatigue symptoms often presented as a lack of energy and motivation strongly associated with deterioration of the quality of life of the affected MS patient. Different fatigue degrees are reported by 75-95% of the patients without a reliable predictor of its presentation and severity [19-28]. Around ten publications and nine clinical trials have investigated the symptoms of chronic fatigue since 2001, and authors have recommended careful assessment of patients with MS for detecting bio-psychological symptoms like spasticity and fatigue. [2-7] Latest publications concerning the positive neuroprotective, anti-inflammatory and immunomodulatory effects of foods containing omega-3 polyunsaturated fatty acids (PUFAs), namely EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), encouraged us to evaluate their nutritional impact and potential benefit in attenuating the fatigue symptoms of patients with RRMS phenotype undergoing disease-modifying therapy. Some contradictions regarding the strength of evidence, the observance of food intake, the supplementation’s quality and content, and the lack of definite European consensus on the most appropriate diet were also reasons for planning the research. [24-31]

**Aims:** (1) To study the effects of a regular diet change by abstaining from high-calorie foods rich in saturated fatty acids and adherence to a moderate-calorie Mediterranean diet rich in omega-3 PUFAs, polyphenols, plant fibers, natural antioxidants and other micronutrients in Bulgarian patients with RRMS; (2) To investigate the indicators of general physical condition, metabolic status, pro-inflammatory cytokines with active dynamics in MS (IL-17A) and the blood levels of EPA/DHA before and at the end of the study in patients on a Mediterranean diet (study group 1) and patients on a regular diet taking APA/DHA supplements (study group 2). (3) To evaluate and compare how appropriate, observable, and valuable the recommended diet and supplementation with EPA/DHA are to attenuate the symptoms of fatigue.

**Working hypothesis:** Moderate lifestyle change through adherence to a seasonally adapted Mediterranean diet, promotion of balanced physical activity and behavioral support by a specialist, compared to the regular diet with additional intake of omega-3 PUFAs, will reduce the complaints of fatigue and will be effective in maintaining optimal physical and metabolic parameters for a better quality of functioning in patients aged 18-65 years with RRMS and symptoms of fatigue.

This pilot investigation presents initial 1-year results clarifying the scientific grounds for further extensive study of the problem.

**MATERIALS AND METHODS:**

**Study design:** An open-label prospective non-randomized observational study, with a 12-week follow-up and outcome-evaluation in two arms of non-therapeutic interventions in patients with RRMS ongoing disease-modifying therapy: adherence to a seasonally adapted Mediterranean diet (study group 1) and regular diet intake with omega-3 PUFA supplementation (study group 2).

**Study centre and participants:** This 12-month pilot study was conducted in 2021 at the Department of Neurology in the Medical University – Pleven, Bulgaria. It was funded by an institutional research grant (Project 19/2020) and approved by the local Ethics Research Committee. Participants, male/female aged 18-65, were randomly selected from the outpatient and inpatient data base of the Neurology Clinic at the University Hospital “Dr Georgi Stranski”-Pleven. The eligibility for patient enrollment in the study was assessed according to the following criteria:

1. Inclusion criteria:
   - Capable male and female adults aged 18-65;
   - Self-determined ethnicity with no restrictions (Bulgarian, Roma, other);
   - Diagnosis RRMS as revised by Tompson et al. in 2017 McDonald’s criteria;
   - Receiving disease-modifying therapy for MS, taken at least three months before the recruitment;
   - Willingness to participate in the study and a priory provided written informed consent.

2. Exclusion criteria:
• Incapacity state;
• Children and elderly people;
• Acute attack of MS or exacerbation of the disease a month before or 30 days after the recruitment;
• Intravenous glucocorticoid therapy before or within 30 days of the beginning of the study;
• Severe somatic illness or mental disorder that would impair the ability to follow the protocol;
• Allergy to fish oil, fish and fish products;
• Alcohol or psychoactive substance abuse;
• Taking other supplements a month before or during the recruitment;
• Pregnancy or planning a pregnancy before and during the study, breastfeeding;
• Reluctance or inability to participate in the study.

Study groups: Study group 1 with a planned assignment of 15 participants on a 3-month seasonally adapted Mediterranean diet without receiving any additional food supplementation; Study group 2 with a planned assignment of 15 participants on a regular diet with EPA/DHA food supplementation containing a recommended source and ratio of omega-3 PUFA’s and vitamin E as a stabilizer.

Materials:
1. Biological materials: Two standard samplings of 7-9 ml venous blood were obtained with a vacutainer on an empty stomach in the morning before the beginning and at the end of the period of adherence to the regimen. After collection, whole blood was centrifuged at 500xg for 20 min. The sample transport and sera isolation in both groups was carried out in parallel over time; residual sera were stored for re-control analysis or future testing as notified in the informed consent;
2. Elisa Kits: Human IL-17 A Elisa Kit 2996 (Diaclon, France), Docosahexaenoic acid (DHA) Elisa Kit (Abbexa, UK), Eicosapentanoic acid (EPA) Elisa Kit (MyBioSource, USA);
3. Laboratory Kits: CRP hs Kit (Roche Diagnostics, Germany), cholesterol, HDL total cholesterol, LDL cholesterol, triglycerides (Roche Diagnostics, Germany) for laboratory monitoring of routine blood parameters.
4. Tanita BC-730 Body Analysis Scale with 10 body analysis values for assessment of weight, body fat, visceral fat, muscle mass, body building value, body water and calories basal metabolic rate;
5. Multimedia reader Mithras LB 943 (Berthold Technologies) for measuring the absorption of probes.

Methods:
1. Clinical methods and validated scales for symptom assessment: Diagnostic interview with coded 10-questions patient chart; Extended Disability Assessment Scale (EDSS); Fatigue Scale for Motor and Cognitive Functions (FSMC); Modified Fatigue Impact Scale (MFIS);
2. Immunological methods for testing and evaluation of biomarkers: Enzyme-linked immunosorbent assay (ELISA) for testing human IL-17A, human EPA and DHA;
4. Statistical methods: Descriptive statistics for evaluating and presenting data in tables, graphics and numerical values by using frequencies, percentages, fractions and/or relative frequencies. Frequency analysis of qualitative variables expressed in absolute and relative frequencies. Variation analysis of quantitative variables expressed in mean ± SE, mean ± SD or median with interquartile range (IQR) for interval variables. Parametric methods for hypothesis testing using Student’s t-test for independent samples and one-way and two-way analysis of variance (ANOVA) for the significance of intergroup differences. Non-parametric methods for hypothesis testing using Pearson’s $\chi^2$ test and Fisher’s exact test (for small samples). Linear mixed models for testing the effects of diet/supplementation on outcomes and time; variables such as age, sex, BMI, smoking status, alcohol consumption, disease modifying drug use, serum levels of IL-17A, EPA and DNA, were assessed for their relationship with the diet outcome. Odds ratio (OR) analysis for testing associations between the exposure and outcome at 95% confidence intervals. Values presented as means at 95% confidential intervals; significance for all statistical tests set at $p<0.05$ (α=95%). Data processing with statistical software IBM SPSS Statistics 19.0 and MS Office Excel 2010.

RESULTS:
Recruitment and demographics: A total of 80 male and female patients aged 18-65 were screened. Of them, 60 patients met the eligibility criteria and were invited to participate in the study. The patients were assigned to the nutritional regimes according to their informed consent and expressed willingness to follow the recommendations and the observation periods. Seventeen participants attended the study centre for complete follow-up, and 13 were only partially observed. Among the reasons for dropping out were the existing limitations for travelling and attending the clinical setting during the COVID-19 pandemic. (fig. 1.)

The baseline demographic and general characteristics of the 30 participants were presented in the patient’s charts at the beginning of the study. All the participants were followed-up by a trained neurologist and nutrition specialist from the research group. The personal information provided was coded for data protection in further analysis. (table 1)

A total of 17 patients attended the study centre for a complete 3-month follow-up and data evaluation. All the patients received a regular disease-modifying therapy with glatiramer acetate, ocrelizumab, peginterferon beta-1a, interferon beta-1b, or dimethyl fumarate as prescribed by the observing neurologist during the entire period of study. Patients were weekly monitored for adherence to the nutritional regimens by email or phone calls conducted by the study neurologists. The remote forms of follow-up helped facilitate dietary information from patients unable to regularly attend the study centre for periodic assessment of their food diaries.
Vital parameters and body composition: Vital parameters of blood pressure, pulse rate (PR) and respiratory rate (RespR) were registered and analyzed in the beginning and at the end of the study. Tanita BC-730 Body Analysis Scale for testing of body composition (weight, body fat, visceral fat, muscle mass, body building value, body water and calories basal metabolic rate) was used at the first and second visit of those participants who fully completed the food regime and presented their filled-in dietary diaries in time. According to the first-visit measurements, there was a statistical difference between the mean values of respiratory rate and some of the body composition parameters in males and females. (Table 2) A statistical difference between the groups for the type of omega 3 PUFAs intake in terms of mean age, mean DHA blood levels, and mean metabolite rate was also found. Patients on the Mediterranean diet were younger (aged 39 vs 48; p=0.02) and with lower DHA levels when compared to the patients on the supplement (704 pg/ml vs 1345 pg/ml; p=0.011) and a lower metabolic rate (p=0.036).
Mediterranean diet, supplementation and fatigue:
The dynamics of all the parameter observed at the first and second visits were compared with Student’s T test for paired samples. There was a statistically significant change in the BMI, the general indicators of fatigue in the FSMC and MFIS scales, the levels of total cholesterol and triglycerides, and the serum concentrations of IL17A, EPA and DHA. The metabolic caloric values were also significantly changed. (table 3) Our results demonstrated significant reduction of fatigue in both FSMC and MFIS scales for patients on a Mediterranean diet and on supplementation. (fig. 3 and 4). The mean decrease of the total MFIS score was significantly higher for patients from the study group 1 (p<0.000). (fig. 4).

Table 2. Vital parameters and body composition values by sex at the first visit.

<table>
<thead>
<tr>
<th>Parameter* Sex code</th>
<th>Male Mean ± SD</th>
<th>Female Mean ± SD</th>
<th>B/w groups P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44.15 ± 7.36</td>
<td>42.82 ± 9.09</td>
<td>0.670</td>
</tr>
<tr>
<td>BMI 1</td>
<td>25.79 ± 3.46</td>
<td>24.70 ± 5.93</td>
<td>0.640</td>
</tr>
<tr>
<td>EDSS</td>
<td>3.46 ± 1.46</td>
<td>3.61 ± 1.47</td>
<td>0.792</td>
</tr>
<tr>
<td>FSMC 1</td>
<td>64.22 ± 21.18</td>
<td>56.87 ± 17.63</td>
<td>0.452</td>
</tr>
<tr>
<td>MFIS 1</td>
<td>30.44 ± 16.43</td>
<td>34.25 ± 16.97</td>
<td>0.646</td>
</tr>
<tr>
<td>Chol 1</td>
<td>5.08 ± 1.43</td>
<td>4.78 ± 1.15</td>
<td>0.536</td>
</tr>
<tr>
<td>LDL 1</td>
<td>3.29 ± 1.25</td>
<td>2.83 ± 0.94</td>
<td>0.257</td>
</tr>
<tr>
<td>HDL 1</td>
<td>1.37 ± 0.36</td>
<td>1.51 ± 0.50</td>
<td>0.385</td>
</tr>
<tr>
<td>TG 1</td>
<td>1.29 ± 0.96</td>
<td>1.22 ± 0.74</td>
<td>0.828</td>
</tr>
<tr>
<td>CRP 1</td>
<td>2.03 ± 2.84</td>
<td>1.39 ± 2.09</td>
<td>0.484</td>
</tr>
<tr>
<td>IL17A 1</td>
<td>106.67 ± 48.69</td>
<td>115.18 ± 33.72</td>
<td>0.576</td>
</tr>
<tr>
<td>EPA 1</td>
<td>1332.31 ± 65.41</td>
<td>1334.35 ± 93.59</td>
<td>0.947</td>
</tr>
<tr>
<td>DHA 1</td>
<td>938.46 ± 803.22</td>
<td>1115.71 ± 638.32</td>
<td>0.771</td>
</tr>
<tr>
<td>Pulse 1</td>
<td>69.33 ± 5.81</td>
<td>73.75 ± 6.48</td>
<td>0.159</td>
</tr>
<tr>
<td>RespR 1</td>
<td>15.89 ± 0.60</td>
<td>16.63 ± 0.58</td>
<td>0.017</td>
</tr>
<tr>
<td>Fat % 1</td>
<td>23.54 ± 5.13</td>
<td>30.24 ± 11.48</td>
<td>0.134</td>
</tr>
<tr>
<td>Bone 1 %</td>
<td>3.12 ± 0.32</td>
<td>2.23 ± 0.22</td>
<td>0.000</td>
</tr>
<tr>
<td>Visceral fat 1 %</td>
<td>9.70 ± 2.69</td>
<td>5.23 ± 3.44</td>
<td>0.009</td>
</tr>
<tr>
<td>Water 1 %</td>
<td>51.86 ± 2.32</td>
<td>48.31 ± 7.55</td>
<td>0.199</td>
</tr>
<tr>
<td>Muscle 1 %</td>
<td>58.70 ± 7.03</td>
<td>42.19 ± 4.19</td>
<td>0.000</td>
</tr>
<tr>
<td>Metabolism 1 (kcal)</td>
<td>1826.22 ± 213.44</td>
<td>1340.12 ± 153.45</td>
<td>0.000</td>
</tr>
<tr>
<td>Metabolic rate 1</td>
<td>48.56 ± 8.75</td>
<td>38.12 ± 16.40</td>
<td>0.117</td>
</tr>
</tbody>
</table>

Table 3. Dynamics of observed paired sample values of basic parameters at the first and second visits.

<table>
<thead>
<tr>
<th>Parameter* Sex code</th>
<th>Mean</th>
<th>SD</th>
<th>Mean SE</th>
<th>P two-tailed</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI 1 – BMI 2</td>
<td>0.95882</td>
<td>1.852</td>
<td>0.44928</td>
<td>0.049</td>
</tr>
<tr>
<td>FSMC 1 – FSMC 2</td>
<td>16.176</td>
<td>11.343</td>
<td>2.751</td>
<td>0.000</td>
</tr>
<tr>
<td>MFIS 1 – MFIS 2</td>
<td>7.118</td>
<td>7.656</td>
<td>1.857</td>
<td>0.001</td>
</tr>
<tr>
<td>EDSS</td>
<td>-0.349</td>
<td>0.748</td>
<td>0.182</td>
<td>0.073</td>
</tr>
<tr>
<td>FSMC 1</td>
<td>-0.062</td>
<td>0.670</td>
<td>0.162</td>
<td>0.706</td>
</tr>
<tr>
<td>Chol 1 – Chol 2</td>
<td>-0.232</td>
<td>0.398</td>
<td>0.097</td>
<td>0.029</td>
</tr>
<tr>
<td>LDL 1 – LDL 2</td>
<td>0.016</td>
<td>0.333</td>
<td>0.081</td>
<td>0.847</td>
</tr>
<tr>
<td>HDL 1 – HDL 2</td>
<td>0.776</td>
<td>2.595</td>
<td>0.629</td>
<td>0.235</td>
</tr>
<tr>
<td>TG 1 – TG 2</td>
<td>94.127</td>
<td>41.027</td>
<td>10.257</td>
<td>0.000</td>
</tr>
<tr>
<td>CRP 1 – CRP 2</td>
<td>-52.176</td>
<td>78.411</td>
<td>19.017</td>
<td>0.014</td>
</tr>
<tr>
<td>IL17A 1 – IL17A 2</td>
<td>-186.235</td>
<td>310.290</td>
<td>75.256</td>
<td>0.025</td>
</tr>
<tr>
<td>EPA 1 – EPA 2</td>
<td>0.959</td>
<td>1.852</td>
<td>0.449</td>
<td>0.049</td>
</tr>
</tbody>
</table>
Pearson’s $\chi^2$ test was applied for comparison of the proportions between the different category variables and the groups by diet and sex. A statistically significant reduction to optimal blood pressure levels was observed in the female group on the Mediterranean diet (two-sided $p < 0.001$). We used a linear regression model with repeated measurements for testing the statistically changed indicators between the two visits to evaluate the impact of the diet type. In general, both diet types almost equally contributed to the observed changes. (fig. 2-7).

**Fig. 2.** Effects of diet on BMI expressed as mean values at the first and second visit.

**Fig. 3.** Effects of diet on fatigue expressed as means of the total FSMC score at the first and second visit.

**Fig. 4.** Effects of diet on fatigue expressed as means of the total MFIS score at the first and second visit.

**Fig. 5.** Effects of diet on the serum level of IL17A expressed as mean values at the first and second visit.

**Fig. 6.** Effects of diet on the serum level of EPA expressed as mean values at the first and second visit.

**Fig. 7.** Effects of diet on the serum level of DHA expressed as mean values at the first and second visit.

<table>
<thead>
<tr>
<th></th>
<th>DHA 1 – DHA 2</th>
<th>Fat 1 – Fat 2 (%)</th>
<th>Visc fat 1 – Visc fat 2 (%)</th>
<th>Muscle 1 – Muscle 2 (%)</th>
<th>Metab 1 – Metab 2 (kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>16.176</td>
<td>0.471</td>
<td>0.653</td>
<td>0.977</td>
<td>32.824</td>
</tr>
<tr>
<td>Mean</td>
<td>11.343</td>
<td>2.813</td>
<td>1.313</td>
<td>2.106</td>
<td>57.520</td>
</tr>
<tr>
<td>Standard Dev</td>
<td>2.751</td>
<td>0.682</td>
<td>0.318</td>
<td>0.521</td>
<td>13.951</td>
</tr>
<tr>
<td>p</td>
<td>0.000</td>
<td>0.500</td>
<td>0.057</td>
<td>0.079</td>
<td>0.032</td>
</tr>
</tbody>
</table>
DISCUSSION:

Our pilot study met the primary investigational aims to evaluate the strong and weak points of the selected factors in terms of their impact on the symptoms of fatigue in patients with RRMS. Generally, the small size of participants is a limitation for the statistical power and can be a potential source for analytical bias. Nevertheless, it facilitates the entire process of observations during the unpredictable restrictions provoked by the COVID-19 pandemic. The single-centre recruitment and follow-up appeared beneficial for the unification of the sample collection, sera processing and material storage by the same trained staff and for better patient-doctor communications at the in person visits as well as the distant sessions.

The protocols for the Mediterranean diet and the balanced composition of EPA/DHA supplements were developed on the basis of previous nutritional studies in patients with MS that had indicated an attenuation of the disease-associated complaints, an improvement of the metabolic status and reduced cardiovascular risk. [22, 25, 27-31] Both nutritional regimens in our investigation have contributed to the optimization of the metabolic parameters and decreased serum levels of IL17, thus confirming data published by other researchers. [26, 28, 29] In our study, the levels of IL17A were equally reduced by both nutritional alternatives which needs to be confirmed by further broader research. The registered FSMC and MFIS score changes demonstrate a tendency of reduction in the fatigue symptoms for patients on a Mediterranean diet and on supplementation, which corresponds with the increased serum levels of EPA and DHA measured at the end of the study. These findings confirm the documented by other authors attenuation in fatigue symptoms by optimising the metabolic parameters. [14-20] Willingness expressed by 88% of the patients to include the Mediterranean diet in their seasonal summer nutrition because of feeling more energetic and less anxious is one of the most clinically significant results of this study. Both regimes were equally effective in their good tolerability and lack of harm.

As far as we know, this is the first Bulgarian study on the problem with original design and pilot results. Although it has its limitations, it supports the focus of our working hypothesis and gives directions for further investigations.

CONCLUSION:

This pilot study will benefit research staff in precise planning of subsequent broader studies on food & lifestyle modifications and the impact on the fatigue symptoms of patients with relapsing-remitting multiple sclerosis. The lack of statistical power is understandable for such a small study sample; however, the demonstrative nutrition tendency in improving the physical status and reducing of cardiovascular risk factors by optimizing the metabolic profile and attenuation of fatigue is strongly encouraging for further investigation. The relevant trend in balancing the level of IL17A reveals potential for more detailed analysis of other disease-specific immunological and pro-inflammatory biomarkers in adult patients with multiple sclerosis.

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