Ketogenic Diet-Based Therapy for Fatigue in Patients with Multiple Sclerosis

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Article

Ketogenic Diet-Based Therapy for Fatigue in Patients with Multiple Sclerosis

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Abstract

Fatigue is a frequent, disabling and difficult to treat symptom of multiple sclerosis (MS). Low grade inflammation and energetic dysfunction have been proposed as mechanisms underlying the pathogenesis of this symptom. Owing to its anti-inflammatory and metabolic properties, there is a rational for ketogenic diet (KD) application in this setting. We conducted a single arm open label interventional study on a strictly selected group of 16 non-obese patients with multiple sclerosis who were prescribed KD for three months. With respect to baseline, at 3 months we observed a significant reduction of fatigue severity scale (5.18 ± 1.02 vs. 4.16 ± 0.98; p = 0.042), Epworth Sleepiness Scale (5.64 ± 2.46 vs. 8.46 ± 3.05; p < 0.001), Pittsburgh Sleep Quality Index (5.64 ± 3.53 vs. 7.62 ± 2.59; p = 0.009), Depression Anxiety Stress Scales-21 depression (3.18 ± 2.93 vs. 6.15 ± 3.81; p = 0.036) and anxiety (5.15 ± 4.10 vs. 1.55 ± 1.92; p = 0.019) sub-scales, and an improvement in energy sub-scale of Multiple Sclerosis Quality of Life-54 (52.49 ± 12.83 vs. 37.43 ± 14.26; p = 0.042). These findings suggest that KD might be useful for the treatment of fatigue and they raise the interest for the use of KD in the treatment of other symptoms frequently encountered in multiple sclerosis.

Keywords: ketogenic diet; ketosis; ketones; multiple sclerosis; fatigue; sleepiness; sleep

1. Introduction

Multiple sclerosis is an inflammatory and demyelinating disease of the central nervous system, characterized by focal lesions mediated by the adaptive immune system and by progressive neurodegenerative processes [1]. MS affects approximately 2.8 - 2.9 million people worldwide [2] and more than 140,000 people in Italy, with approximately 3,600 new diagnoses each year. The prevalence is around 227 cases per 100,000 inhabitants in mainland Italy and predominantly involves women, with a female-to-male ratio of about 3 to 1. Diagnosis typically occurs in young adulthood, between 20 and 40 years of age [3]. Fatigue is the most common symptom in patients with MS, with ad incidence of up to 90% of patients, having often a significant impact on everyday life activities [4,5]. In MS, chronic fatigue has been defined as "fatigue that is present for any amount of time on 50% of days for more than 6 weeks, that limits functional activities or quality of life" Multiple Sclerosis Council [6].

Disease-modifying therapies (DMTs) are currently the gold standard for the treatment of MS and their effectiveness has been assessed through randomized clinical trials (RCTs). However, there is limited information regarding the impact of DMTs on fatigue in patients with Multiple Sclerosis (pwMS) [7]. Consequently, increasing attention has been directed toward non-pharmacological interventions aimed at improving fatigue and quality of life in pwMS [8].

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Starting from the recognition of the so called "sickness behaviour" induced by pro-inflammatory cytokines, some observations suggest that inflammation may be one of the processes underlying fatigue [9]. Moreover, patients with conditions associated with fatigue, such as chronic fatigue syndrome and depression, may present altered levels of cytokines in the peripheral circulation, generally expressing a predominant Th1 pro-inflammatory profile [10]. Many studies have suggested higher levels of pro-inflammatory factors also in fatigued pwMS, although there are also some negative findings [11,12]

Another aspect of interest in fatigue pathogenesis is the possible existence of an energetic dysfunction in the CNS of MS fatigued patients, as suggested by some imaging [13,14] and laboratory findings. Demyelination in MS causes important changes from the neuronal energetic point of view, given that the loss of saltatory conduction determines a greater need for ATP consumption by Na+/K+ ATPase. In addition, the mitochondrial damage secondary to the inflammatory process contributes to create this unfavourable energetic state which has been defined "virtual hypoxia" [15–18].

Considering these premises, intervention with anti-inflammatory properties and the ability to restore CNS energetic dysfunction may be a reasonable option for fatigue treatment.

Ketogenic diet (KD) is a nutritional strategy initially introduced by Russell Wilder in 1920 as a non-drug treatment for epilepsy. He also coined the term "ketogenic diet" at that time [19,20]. This diet gained popularity in the 1970s, emerging as a potential therapy for various health conditions and as an effective short-term approach to weight loss [21,22]. By drastically reducing carbohydrates intake and increasing the consumption of fats and proteins, this dietary approach induces a metabolic state known as "ketosis", where fats become the primary energy source instead of carbohydrates.

Recent research highlights the potential benefits of ketogenic diet in lowering the risk of certain diseases, including type 2 diabetes, hyperlipidemia, cardiovascular conditions, and cancer [23]. The ketogenic diet is characterized by a high intake of fats, a moderate amount of protein, and a low consumption of carbohydrates. Typically, the macronutrient composition includes fats making up 60-90% of the total energy intake (commonly 70-75%), carbohydrates limited to less than 50g per day (about 5-10% of total caloric intake), and proteins ranging from 1.0-1.2 to 1.7 grams per kilogram of body weight (accounting for around 20% of daily caloric intake) [24].

The primary objective of all ketogenic diets (KDs) is to stimulate ketone production while ensuring that the body receives adequate caloric intake. KDs exhibit notable anti-inflammatory properties through various molecular pathways and have shown promising results in the management of neurological conditions in which inflammation plays a key role [25].

Additionally, ketone bodies generated during this diet serve as a highly efficient energy source, significantly increasing the ATP/ADP ratio in the brain [17,20]. Ketone bodies are also preferred energy substrate for oligodendrocytes, supporting energy production and myelin synthesis [26,27].

The effect of KD on sleep quality and daytime somnolence has been examined in an exploratory study of patients affected by Multiple Sclerosis [28,29].

Building on this theoretical foundation, the present study aimed to assess the effects of KD on fatigue and other symptoms, such as sleepiness and sleep disturbances, in a carefully selected group of individuals with MS.

2. Materials and Methods

2.1. Study Design and Participants

This was a prospective, single-center, non-pharmacological study conducted in volunteers.

From January 2020 to November 2022, we selected and enrolled patients who attended our multiple sclerosis and demyelinating diseases clinic (Clinical Neurology Unit, S. Maria della Misericordia University Hospital, Udine, Italy).

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2.2. Inclusion and Exclusion Criteria

Participants were individuals with relapsing-remitting multiple sclerosis (RRMS) who were non-disabled or minimally disabled according to the 2017 McDonald criteria [30], who were treated with disease-modifying therapies (DMTs) for at least one year, and had no clinical or neuroradiological relapses in the six months prior to or during the study. Additionally, participants had no significant contraindications to the ketogenic diet (KD).

We excluded patients with conditions that could interfere with sleep and fatigue in individuals with MS, including those at intermediate or high risk for obstructive sleep apnea (OSA) as assessed by the STOP-Bang questionnaire [31], those who met the international diagnostic criteria for restless legs syndrome (RLS) [32], and patients diagnosed with depressive or anxiety disorders according to the DSM-V criteria [33,34]. Furthermore, patients taking antidepressants, benzodiazepines, or other sedative medications were excluded from the study.

Table 1. inclusion and exclusion criteria for study participation.

Inclusion Criteria	Exclusion Criteria
Diagnosis of (RR)MS following revised McDonald criteria (CIT)	Renal failure (estimated glomerular filtration rate with Cockroft-Gault formula < 60 ml/min)
Age between 18 and 65 years	History of urinary stone
EDSS < 2.5 at enrolment	Hepatic failure
Patients on DMD for at least 1 year	Known cardiopathies
In treatment with one of the following DMDs: glatimer acetate, teriflunomide, dimethyl fumarate, interferons	History of arrhythmia or conduction abnormalities on baseline electrocardiogram (not including right branch block and type I atrio-ventricular block)
Clinically relevant fatigue (FSS ≥ 4)	Diabetes mellitus
BMI between 19 and 35 kg/m^2	Porphyria
	Known deficit of pyruvate carboxylase
	Known disorders of lipid metabolism
	Ischaemic stroke or transient ischaemic attack in the previous 6 months
	Pregnancy and lactation
	History of acute or chronic pancreatitis
	Severe osteoporosis
	Known thyroid disfunction
	Alcohol abuse
	Eating disorders
	Diagnosis of epilepsy or seizure in the past 2 years
	Diagnosis of major depressive disorder

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	Treatment with anti-depressants, benzodiazepines or hypnotic drugs
	Relapses of MS in the last 6 months
	Steroid treatment in the last 6 months
	New MRI demyelinating lesions in the previous 6 months

2.3. Ethical Aspects

Patients were provided with comprehensive written information about the study, including details on the study design, expected benefits, and potential adverse events associated with the ketogenic diet (KD). All patients provided written informed consent to participate in the study. The study was conducted in accordance with the Declaration of Helsinki and approved by the Comitato Etico Unico Regionale del Friuli Venezia Giulia (CEUR-2020-SPER-124).

2.4. Dietetic Intervention and Nutritional Evaluations

Following enrolment, each patient underwent an initial nutritional assessment, during which height, weight, and Body Mass Index (BMI) were recorded. Body composition was assessed using bioelectrical impedance analysis with the BIA 101 BIVA PRO (Akern) device. Based on these data and the individual characteristics of each patient, a 2:1 ketogenic diet was prescribed, which patients were instructed to follow for three months, provided it was well tolerated.

The dietary regimen was individualized according to patients' preferences and body composition parameters (BMI, Fat Mass and Fat Free Mass). The protein and fat content of each diet was determined using anthropometric measurements, bioelectrical impedance data, and the patient's daily level of physical activity. Carbohydrate intake was fixed at 30g/day. Protein intake was calculated primarily on the basis of fat free mass (FFM), with conversion into grams taking into account activity level and ideal body weight.

Patients were re-evaluated after 1 and 3 months from the start of the diet. During follow-up visits, anthropometric and body composition measurements were repeated; adherence to the dietary regimen was assessed, and practical advice was provided to improve correct implementation. To ensure adherence to the ketogenic dietary plan, patients were instructed to measure capillary blood ketone levels at least twice per week. Finally, telephone support was made available throughout the entire intervention period to address any diet-related questions or concerns.

2.5. Outcomes

Clinical and demographic characteristics were collected at baseline. Data regarding adverse events or relapses were collected during follow-up by means of monthly phone calls and subsequent medical examination, if deemed necessary by study investigators.

The primary objective of the study was to assess the change in fatigue severity from baseline to 3 months, as measured by the Fatigue Severity Scale, in a group of patients with relapsing remitting multiple sclerosis undergoing a ketogenic diet.

Secondary objectives were to evaluate, in the same patient population, the differences between baseline and the 3-months follow-up with respect to the following aspects: sleep quality, mood disturbances and quality of life. Thus, at baseline and 1 and 3 months after diet initiation, the following questionnaires were administered, all in their validated Italian version: Fatigue severity scale (FSS) [35,36], Epworth Sleepiness Scale (ESS)[37,38], Pittsburgh Sleep Quality Index (PSQI) [39,40], Depression Anxiety Stress Scales-21 (DASS-21)[41,42], Multiple Sclerosis Quality of Life-54 (MSQOL-54) [43,44].

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2.6. Fatigue Severity Scale (FSS)

Fatigue is a symptom assessed through self-reporting. The Fatigue Severity Scale (FSS) is a 9-item tool that evaluates the average level of fatigue experienced by patients in the previous days. It gauges both the intensity of fatigue and its impact on a person's daily activities and quality of life under various conditions. Originally developed for multiple sclerosis and systemic lupus erythematosus, it has also been applied to migraines *[45]*. This scale assesses how fatigue in chronic conditions affects cognitive and physical functioning. Patients rate the severity of their fatigue symptoms for each item, with lower scores indicating disagreement and higher scores indicating agreement. Each statement is scored on a 7-point scale, from 1 (strongly disagree) to 7 (strongly agree). The total score is calculated by summing the individual responses and dividing by nine, although some studies use the total sum score instead. A score of at least 4 (or 36) is considered indicative of pathological fatigue *[46].*

2.7. Pittsburg Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS)

The Epworth Sleepiness Scale (ESS) is a questionnaire widely used worldwide to subjectively assess the tendency to fall asleep in specific daytime situations, such as reading, watching TV, or being a passenger in a car.

The ESS is an 8-item test developed by Murray J. in 1991 *[47]*. It is self-administered and provides a score on a numerical scale ranging from 0 to 24. A score greater than 10 is generally accepted as indicative of Excessive Daytime Sleepiness.

The PSQI (Pittsburgh Sleep Quality Index) is a rating scale designed to provide a reliable, valid, and standardized measure of sleep quality. The scale consists of 19 items self-assessed by an individual. These 19 items are grouped into seven composite components that represent subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of hypnotic medication, and daytime dysfunction [48].

2.8. Data and Statistical Analysis

Statistical analysis was performed using JASP version 0.14.1 for macOS (University of Amsterdam, Netherlands). A descriptive analysis was conducted to report the means and standard deviations. The Shapiro-Wilk test correction was used to assess the normal distribution of the data. For comparisons between baseline and following time points, the paired samples t-test or Wilcoxon's test was used as appropriate. Two-tailed p-values of <0.05 were considered statistically significant.

3. Results

Sixteen patients were enrolled in this study at the end of February 2023.

Eleven (68.75%) patients were females and five (31.25%) were males. Mean age was 46.31±10.63 years, and mean time from MS diagnosis was of 10.31±7.14 years. All patients had a basal EDSS scores between 1 and 2. The DMDs distribution was as follow: 7 (43.75%) dimethyl fumarate, 3 (18.75%) teriflunomide, 3 (18.75%) glatiramer acetate, and 3 (18.75%) interferons.

Four patients did not complete the 3 months study period. One patient stopped the study because of difficulties in following the diet due to the necessity of frequently not eating at home for work reasons, and one found the diet too restrictive. Two patients abandoned the diet due to side effects: one patient experienced weight loss that was perceived as excessive by the patient, but with a BMI still in the range of normality, while another reported abdominal pain soon after diet initiation.

In addition to the cases that dropped due to excessive weight loss and abdominal pain, other adverse events reported by the patients included: dermatitis, observed in one patient, which resolved in a few days and was considered by the investigators not related to the diet; and muscle cramps, observed at the third month of diet in one patient who was not correctly assuming the prescribed food supplement and resolved after it was correctly assumed.

None of the patients experienced an MS relapse during the 3 months of diet.

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Considering our primary outcome of fatigue, we observed a trend for reduction in FSS scores after 1 month of diet (4.16±1.37 vs. 5.18±1.02; p=0.052) which became significant at 3 months (4.16±0.98 vs. 5.18±1.02; p=0.042). Considering the other outcome measures, ESS scores also improved reaching a statistically significant reduction at 3 months. The PSQI and the subscales for depression and anxiety of the DASS-21 all showed a better score during KD with a significant reduction at both 1 and 3 months. The stress subscale of the DASS-21 showed an initial improvement which was not consistent at 3 months. Table 1 shows the results of the fatigue, sleep and mood scales during the diet.

Table 1. Results of questionnaires at baseline and after one and three months of KD. Results are expressed as means±SD. P values reported are expression of a paired sample comparison between baseline and the considered time-point. FSS: Fatigue Severity Scale; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index; DASS 21: Depression Anxiety Stress Scale 21.

	Baseline (mean±SD)	1 month (mean±SD)	3 months (mean±SD)
FSS	5.18±1.02	4.16±1.37; p=0.052	4.16±0.98; p=0.042*
ESS	8.46±3.05	7.20±4.19; p=0.127	5.64±2.46; p<0.001*
PSQI	7.62±2.59	5.50±3.27; p=0.011*	5.64±3.53; p=0.009*
DASS-21 depression	6.15±3.81	2.50±3.95; p=0.045*	3.18±2.93; p=0.036*
DASS-21 anxiety	5.15±4.10	1.70±2.31; p=0.033*	1.55±1.92; p=0.019*
DASS-21 stress	9.15±4.51	3.60±4.09; p=0.003*	6.273±4.63; p=0.208

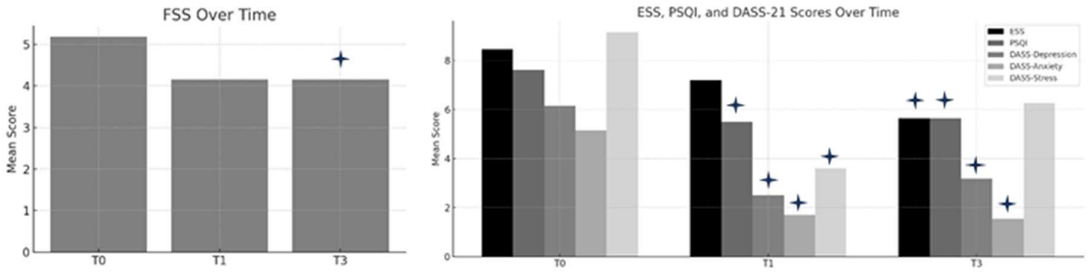

Figure 1. Results of questionnaires at baseline and after one and three months of KD. Results are expressed as means±SD. P values reported are expression of a paired sample comparison between baseline and the considered time-point. FSS: Fatigue Severity Scale; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index; DASS 21: Depression Anxiety Stress Scale 21. Significant results.

Despite a trend toward better scores, we did not observe any significant modification of the physical health composite score or mental health composite scores of the MSQOL-54. The only MSQOL-54 subscale that showed a significant change from the baseline was that of energy at 3 months (37.43±14.26 at baseline, 52.49±12.83 at three months, p=0.042). Table 2 shows the MSQOL-54 subscales variations during the study period.

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Table 2. MSQOL-54 subscales scores at baseline and after different months of KD. Results are expressed as means±SD.

	Baseline (mean±SD)	1 month (mean±SD)	3 months (mean±SD)
Physical health	78.57±16.81	85.46±10.59; p=0.057	84.09±13.38; p=0.146
Role limitations due to physical problems	41.07±38.74	77.27±28.41; p=0.148	72.73±34.38; p=0.138
Role limitations due to emotional problems	50.00±48.48	75.76±36.79; p=0.191	66.67±42.16; p=0.893
Pain	70.64±22.31	80.30±18.47; p=0.400	84.85±19.73; p=0.172
Emotional well-being	58.57±16.12	69.46±17.28; p=0.128	67.09±16.13; p=0.314
Energy	37.43±14.26	50.90±17.54; p=0.056	52.49±12.83; p=0.042*
Health perceptions	45.71±17.08	53.18±13.65; p=0.271	52.78±14.73; p=0.276
Social function	66.67±21.68	82.58±15.57; p=0.072	82.58±16.86; p=0.288
Cognitive function	66.07±18.42	72.27±12.12; p=0.125	75.00±15.65; p=0.120
Health distress	73.21±15.01	78.64±12.67; p=0.916	78.18±13.83; p=0.945
Sexual function	69.23±30.13	64.82±33.02; p=0.732	75.00±28.87; p=0.138
Change in health	44.64±20.05	56.82±22.61; p=0.414	61.36±23.36; p=0.177
Satisfaction with sexual function	53.57±32.31	50.00±35.36; p=1.000	56.82±33.71; p=0.726
Overall quality of life	63.33±16.27	69.88±12.97; p=0.629	72.39±13.76; p=0.207
Physical health composite score	60.87±12.91	73.32±11.34; p=0.316	72.18±13.22; p=0.178
Mental health composite score	59.90±15.35	72.75±14.95; p=0.130	69.77±17.72; p=0.770

From a nutritional point of view, we observed a significant reduction in body mass index (BMI) and fat mass (FM) at both 1 and 3 months, while lean mass was preserved at 1 month and even increased after 3 months of KD (Table 3)

Table 3. nutritional data at baseline and after 1 month of KD. Results are expressed as means±SD.

	Baseline (mean±SD)	1 month (mean±SD)	3 months (mean±SD)
Body Mass Index (BMI) (kg/m2)	23.54±2.98	22.56±2.49; p=0.004*	23.26±2.04; p=0.004*
Fat mass (kg)	18.73±8.26	16.31±7.70; p=0.002*	17.43±7.70; p=0.034*
Lean mass (kg)	49.52±8.37	47.67±6.24; p=0.064	49.94±8.43; p=0.010*
Intracellular water (L)	18.99±4.42	18.87±4.65; p=0.248	19.30±4.25; p=0.059
Extracellular water (L)	17.33±2.05	17.21±5.58; p=0.170	17.31±2.22; p=0.014*

4. Discussion

In the present study, 4 of 16 patients (25%) discontinued the diet because of tolerability issues. Globally, these are good adherence rates, since in the setting of epilepsy a 2014 review that considered only adults found a drop-out rate of 51% when considering classic KDs and of 42% when considering

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a modified Atkins diet [49]. In our experience, in a group of patients affected by migraine, treated with a KD with the same ketogenic ratio, we observed a dropout rate of 18%, which is quite similar to the findings of the present study [50], thus not suggesting specific limitations of application of this approach in the MS population.

All the side effects observed in our study were transient, and KD was discontinued because of adverse events only in two cases. Muscle cramps and excessive weight loss are frequent side effects of KD, and abdominal pain has also been described, although more rarely [51]. The dermatitis reported was not deemed related to KD by the study investigators.

We did not observe any clinical relapse of MS during the study period. In the previous studies using ketogenic diet in MS, Choi et al. reported only one relapse in their group of 20 patients, while Brenton et al. did not observe relapses in their group of 56 patients [52,53]. Both studies lasted for 6 months. The small number of patients considered in these studies and in our study and the short time of observation make ~~it~~ impossible any consideration about diet efficacy in reducing the relapse rate in MS.

Considering our primary outcome measure, we observed a reduction in fatigue as measured by FSS, which was statistically significant after 3 months of diet. Similarly, we observed an improvement at 3 months in the energy subscale of the MSQOL-54. To our knowledge, two studies by the same American group have evaluated the effect of KD on MS symptom, with similar positive results [52,54]. However, since in both studies the majority of the sample was formed by overweight or obese patients [52,54], and given that higher BMI has been associated with higher fatigue scores both in pwMS [55] and in people not suffering from this disease [56], the findings of these studies must be taken with caution. It must also be noted that in these studies the dietary intervention was very simple, and subjects were only instructed to restrict carbohydrates to <20 g/day and to consume more healthy fats [52]. The results of our study, which excluded obese patients and instructed patients to follow a precise diet regimen, offer amore robust evidence of the usefulness of KD in reducing the disabling symptom of fatigue in pwMS.

We also observed a consistent reduction in excessive daytime sleepiness as measured by ESS, and an improvement in sleep quality as measured by PSQI. To our knowledge, this is the first study to assess sleep in patients with pwMS receiving KD, although sleep disturbances are a common problem in the MS population [57,58]. In addition, also considering the application of KD in other settings, data about sleep and sleepiness remains scarce [59,60].

Many mechanisms by which KD may act on sleep have been proposed, including orexinergic neurons activation by means of relative hypoglycaemia provoked by KD, an increase in galanin expression and consequent monoaminergic arousal systems inhibition or an increase in the GABA/glutamate ratio [61–64].

In our study, we found that patients with MS and KD showed a significant reduction in depression and anxiety scores. Considering KD studies in patients with MS, the only other studies that evaluated the effect of this dietary approach on mood disturbances are those already mentioned by Brenton et al. [52,65], in which pwMS receiving a KD reported a reduction in Beck Depression Inventory scores. In addition to MS, KD has been shown to improve negative affect also in overweight but otherwise healthy patients [66] and in a mixed cohort of psychiatric inpatients [67]. KD application in the treatment of depression and anxiety is supported also by animal data [68,69]. The mechanism by which KD ameliorates depression and anxiety is not clear, but modulation of GABAergic and monoaminergic systems may be involved, along with chronic low grade inflammation reduction and mitochondrial function restoration [70,71]. Our finding of a reduction in depression and anxiety symptoms in pwMS receiving a KD are relevant in relation to the extent of the phenomenon, since depression and anxiety prevalence among pwMS can be as high as 30.5% and 22.1% respectively [72], and depression, together with fatigue and disability, is one of the most important determinants of quality of life in these patients [73].

Although an in-depth description of the effect of KD on weight and fat mass reduction is beyond the scope of this study, we have at least to comment that the observed reduction in BMI and FM with

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lean mass preservation corroborates the already known possibility of KD utilization for weight loss [74,75]. As previously discussed, we did not include obese patients in this study, and the median BMI of the study group was within the normal range before and after the dietary intervention.

5. Conclusions

After the great results reached in the prevention of relapses and disability worsening in MS with the introduction of many disease modifying drugs, the research focused on treating more subtle, but still very disabling symptoms, such as fatigue. Although the exact processes behind this symptom remain partially unclear, persistent inflammation and neuronal energetic dysfunction are suggested to be involved [76–78]. In this study, we aimed to evaluate the application of KD in a group of RRMS patients, given the anti-inflammatory and energetic properties of this diet [79].

First, we found that ketogenic intervention is applicable to MS patients with limitations similar to those of other dietary interventions and with a higher adherence than that described for KD in other disorders.

Regarding our primary outcome, we observed an improvement in fatigue during KD. In parallel, KD resulted in the significant amelioration of sleep and daytime somnolence, and a reduction in depression and anxiety symptoms.

We are aware that the present study has several limitations. First, the sample size was limited and, given the chronic nature of MS, longer observation times are required to assess long-term efficacy and tolerability of KD. Another limitation is the lack of a control group. The use of laboratory and instrumental outcomes may also help corroborate KD utilization in this field, and studies including these targets are ongoing at our center.

The present study also has some strengths, dependent on accurate the sample selection, which gave us the possibility of excluding many confounding factors, and on the precise diet prescriptions adopted.

Further studies with longer follow-up periods, larger sample sizes and a control group are needed to firmly establish KD efficacy on MS symptoms and course.

Author Contributions: F.F: Conceptualization, Investigation, Data Curation, Visualization, Writing—Original Draft, Statistical Analysis, Project Administration; S.L.: Writing—Review and Editing, Statistical Analysis; R.G.: Investigation, Data Curation; E.L.: Investigation, Data Curation; I.D.N.: Investigation, Data Curation; A.N.: Investigation, Data Curation; S.P.: Investigation, Data Curation; G.L.G.: Conceptualization, Supervision, Resources, Validation, Writing—Review and Editing; M.V.: Conceptualization, Supervision, Resources, Validation, Writing—Review and Editing, Project Administration. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Unique Regional Ethics Committee of Friuli Venezia Giulia on November 17th 2020, approval code CEUR-2020-SPER-124.

Informed Consent Statement: All patients involved in the study gave written informed consent for study participation.:

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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Abbreviations

MS	Multiple Sclerosis
KD	Ketogenic Diet
DMTs	Disease-Modifying Therapies
RCTs	Randomized Clinical Trials
pwMS	Patients With Multiple Sclerosis
CNS	Central Nervous System
RRMS	Relapsing Remitting Multiple Sclerosis
FSS	Fatigue Severity Scale
ESS	Epworth Sleepiness Scale
PSQI	Pittsburg Sleep Quality Index
DASS-21	Depression Anxiety Stress Scale-21
MSQOL-54	Multiple Sclerosis Quality of Life - 54
BMI	Body Mass Index
BIA	Bioelectrical Impedance Analysis
FM	Fat Mass
FFM	Fat Free Mass

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