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Ketogenic diet may improve sleep quality and daytime somnolence in patients affected by multiple sclerosis. Results of an exploratory study

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ABSTRACT

Objective/background: Patients with multiple sclerosis (MS) frequently report sleep complaints. The ketogenic diet (KD) is safe and tolerable in MS patients. Our aim was: 1) to investigate the effects of KD on sleep complaints in patients affected by relapsing-remitting MS and 2) to verify if sleep changes can positively impact on psychological status and quality of life (QoL) in these patients.

Patients/methods: From January 2020 to November 2022, we consecutively enrolled 21 non-disabled or minimally disabled MS patients. We collected information regarding: 1) anthropometric measures; 2) psychological status by the Depression Anxiety Stress Scale-21; 3) QoL by the Multiple Sclerosis Quality of Life-54 (MSQOL-54); 4) subjective sleep complaints, i.e. sleep quality, by the Pittsburgh Sleep Quality Index (PSQI), and excessive daytime sleepiness (EDS), by the Epworth Sleepiness Scale (ESS).

Results: After 6 months of KD therapy, anthropometric measures considerably changed, psychological status significantly improved, and almost all the MSQOL-54 subscales ameliorated. Regarding sleep, we observed that the global PSQI (T0: 7.7 ± 3.1 versus T1: 4.4 ± 3.1, $p = 0.002$) and the ESS (T0: 7.5 ± 3.9 versus T1: 4.9 ± 3.2, $p = 0.001$) scores significantly decreased after KD therapy. At T1, only the global PSQI score was an independent predictor of anxiety, stress, and mental health.

Conclusions: For the first time, we demonstrated that KD may improve sleep complaints in MS patients. In addition, KD seems to have a positive impact on psychological status and QoL of MS patients, mainly through improving sleep quality. Further controlled studies with larger sample sizes are needed to confirm these preliminary results.

1. Introduction

Sleep is essential for brain function and acute lack of sleep leads to impaired memory and attention, while chronic sleep deprivation produces neurological dysfunction or even death [1]. Moreover, sleep disruption has harmful consequences on metabolic, endocrine, and cardiovascular systems [2]. This essential physiological process is largely compromised in multiple sclerosis (MS) patients.

MS is an immune-mediated inflammatory disorder of the central nervous system with a highly variable course involving different areas of brain, spinal cord, and optic nerves and causing impairment in mobility, balance, sensation, sphincter control, vision, and cognition [3]. Sleep disorders are common in MS, affecting 25 %–54 % of patients with this demyelinating disease [4]. Indeed, insomnia, sleep-disordered breathing, circadian rhythm disorder, restless legs syndrome (RLS), narcolepsy, and rapid eye movement (REM) sleep behavior disorder have all been reported in the MS population [4]. Moreover, almost 50 % of MS patients report poor sleep quality that seems to impair their quality of life (QoL) [5].

Ketogenic diet (KD) is a high-fat, low-carbohydrate diet that stimulates the synthesis of ketone bodies as a source of energy. KD has traditionally been used to treat resistant epilepsy, but it is increasingly

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becoming apparent that its benefits may apply to a broader spectrum of neurological diseases. In particular, a phase II study demonstrated that KD is safe and tolerable, yielding improvements in body composition, fatigue, depression, QoL, neurological disability, and adipose-related inflammation in patients with relapsing-remitting MS [6]. Recently, we reported the beneficial effects of KD on sleep complaints in migraine subjects [7]. Based on these suggestions, we decided to perform an exploratory study investigating the effects of KD on sleep complaints in a highly selected population of MS patients. Moreover, we examined if KD, as a result of improved sleep, can positively impact on psychological status and QoL in these patients.

2. Material and methods

2.1. Patients

From January 2020 to November 2022, we enrolled 21 consecutive patients who attended our multiple sclerosis and demyelinating diseases clinic (Clinical Neurology Unit, S. Maria della Misericordia University Hospital, Udine, Italy) and satisfied the inclusion and exclusion criteria reported in Table 1. Shortly, we included non-disabled or minimally disabled patients affected by relapsing-remitting MS, based on the 2017 McDonald criteria [8], treated with disease-modifying drugs (DMDs) for at least one year, without clinical or neuroradiological relapses in the previous 6 months and during the study period, and with no significant contraindications for KD. Since the following clinical conditions can disrupt sleep in MS patients, we excluded: subjects with an intermediate or high risk for obstructive sleep apnea (OSA), based on the STOP-Bang questionnaire [9], who satisfied the international clinical criteria for RLS diagnosis [10], and patients with a DSM-V diagnosis of depressive or anxiety disorder [11]. In addition, subjects treated with antidepressants, benzodiazepines, or other hypnotic drugs were excluded. During the study period, we excluded 6 patients because of lack of adherence to diet regime and 2 patients with clinical relapsing.

The following data were collected: demographic characteristics (gender and age), duration of MS, EDSS score assigned by a blinded clinical neurologist [12], and therapeutic information.

Patients received complete written information about the study, including information about study design, expected benefits, and possible adverse events during KD. All the patients gave written informed consent for study participation. 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).

Table 1
Inclusion and exclusion criteria for study participation.

Inclusion criteria	Exclusion criteria
• Age between 18 and 65 years • Diagnosis of relapsing-remitting MS • EDSS score <2.5 at the enrollment • Use of DMDs for at least one year • BMI between 19 and 30 kg/m^2	• Clinical or radiological relapses in the previous six months and during the study period • Steroid treatment in the last six months • DMDs discontinuation or dose modification during the study period • Renal failure (estimated glomerular filtration rate <60 ml/min) • History of urinary stones • Hepatic failure • Known cardiopathies • History of arrhythmia or conduction abnormalities on baseline electrocardiography (not including right branch block and type I atrioventricular block) • Diabetes mellitus • Porphyria • Known deficit of pyruvate carboxylase • Known disorders of lipid metabolism • Ischemic stroke or transient ischemic attack in the previous 6 months • Pregnancy and lactation • History of acute or chronic pancreatitis • Severe osteoporosis • Known thyroid disfunction • Alcohol abuse • Eating disorders • Intermediate or high risk for obstructive sleep apnea (STOP-Bang score >2) • Presence of RLS • DSM-V diagnosis of depressive or anxiety disorder • Use of antidepressants, benzodiazepines, or other hypnotic drug

MS: multiple sclerosis; EDSS: Expanded Disability Status Scale; DMDs: disease-modifying drugs; BMI: body mass index; RLS: restless legs syndrome; DSM-V: Diagnostic and Statistical Manual of Mental Disorders, fifth edition.

2.2. Ketogenic diet

After enrollment, a first nutritional evaluation was performed in which height, weight, and BMI were collected. Bioimpedance analysis using BIA 101 BIVA PRO (Akern®) was also performed to determine fat mass (FM), and fat-free mass (FFM). A 2:1 KD was prescribed and tailored to the patient's characteristics. In this KD protocol the number of fats equals double the sum of carbohydrates and proteins. The total calories of this diet are 1600–2300 Kcal/day. The quantity of carbohydrates is fixed at 30 g per day. Adequate food supplements specific to the KD, i.e. multivitamin/mineral supplements, were provided to all the patients in the study. Patients were instructed to follow the diet for 6 months. A phone contact was provided to patients in case of questions relative to the diet. Differently from a previous study that used daily urine ketone test strips for monitoring KD adherence [6], we implemented a weekly telephone intervention led by a nutritionist to identify instances of non-adherence to the KD. As reported above, we excluded 6 non-adherent patients during the study period.

2.3. Psychological status

We collected information on symptoms of depression, anxiety, and stress using the Italian validated version of the Depression Anxiety Stress Scale-21 (DASS-21) [13].

The DASS-21 contains three subscales (depression, anxiety, stress), each containing seven items. The depression subscale evaluates dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia, and inertia. The anxiety subscale measures autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. The stress subscale is sensitive to chronic non-specific arousal levels and evaluates difficulty relaxing, nervous arousal, and being easily upset/agitated, irritable/over-reactive, and impatient. For each item, the participant has to read each statement applied to him/her over the past week that best describes his/her condition and answer on a four-point Likert scale (0 = did not apply to me at all, 1 = applied to me to some degree or some of the time, 2 = applied to me to a considerable degree or a good part of the time, 3 = applied to me very much or most of the time). The sum of all items on each subscale yields a scale's score result verified with the cut-off scores for conventional severity labels (normal, moderate, severe, extremely severe) on the depression, anxiety, and stress scale according to Manual for the Depression Anxiety & Stress Scales [14].

2.4. Quality of life

The Italian validated version of the Multiple Sclerosis Quality of Life-54 (MSQOL-54) was used to measure QoL in our sample of MS patients [15].

The MSQOL-54 is a multidimensional, MS-specific health-related quality of life instrument based on the generic SF-36 [16] supplemented with 18 MS-specific items [17]. It consists of 52 items combined in 12 subscales (physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health

perception, social function, cognitive function, health distress, overall quality of life, and sexual function) and two single items (satisfaction with sexual function and change in health). Two composite scores (Mental Health Composite, MHC, and Physical Health Composite, PHC) are determined by aggregating scores of the pertinent subscales. Higher scores indicate better QoL.

2.5. Sleep evaluation

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a self-administered questionnaire validated to assess sleep quality during the previous month. It contains 19 self-rated questions, yielding seven components: C1 = sleep quality, C2 = sleep onset latency, C3 = sleep duration, C4 = sleep efficiency, C5 = sleep disturbance, C6 = use of hypnotic drugs, and C7 = daytime dysfunction. Each component is scored between 0 and 3, yielding a global PSQI score ranging from 0 to 21, with a higher score indicating a lower sleep quality. A global PSQI score >5 was adopted to measure poor sleep [18]. The Italian validated version of the PSQI was adopted for this study [19].

To evaluate the presence of excessive daytime sleepiness (EDS), patients had to fill in the Italian version of the Epworth Sleepiness Scale (ESS). Subjects reporting an ESS score ≥10 were identified as affected by EDS [20].

2.6. Study protocol

Information on sleep features was collected before the starting of KD therapy (T0) and after 6 months of treatment (T1). Similarly, anthropometric data and results of the DASS-21 and the MSQOL-54 were calculated at T0 and T1.

2.7. Statistical analysis

Normal distribution was tested by means of the Kolmogorov-Smirnov test. Differences regarding anthropometric measures, sleep characteristics, psychological status, and QoL between T0 and T1 were assessed by the McNemar test for categorical variables and the paired *t*-test or the Wilcoxon test, when appropriate, for continuous variables. Using the Spearmen correlation test, we tested if the global PSQI and ESS scores were correlated with the anthropometric measures, psychological status, and QoL at T1. To verify if the global PSQI and ESS scores were independent predictors of psychological status and QoL at T1, a multivariate linear regression with forward stepwise selection ($\alpha = 0.05$), including the sleep features and other variables, such as age, sex, duration of MS, and EDSS score, was performed. To reduce the number of regressions, we used MHC and PHC scores as outcome variables rather than the scores of each MSQOL-54 subscale. The data are presented in tables as mean and standard deviation, if not otherwise specified. $P < 0.05$ was considered statistically significant. Statistical analysis was carried out using SPSS 26.0 software.

As no data have been published on the effects of KD on sleep in MS patients, this study is exploratory. Therefore, no statistical power calculation was conducted prior to the study.

3. Results

3.1. General characteristics

The 21 patients enrolled in this study, 15 females and 6 males, had a mean age of 48.3 ± 9.8 years. The mean MS duration was 10.9 ± 7.2 years. All patients had a basal EDSS value comprised between 1 and 2. The following DMDs were used for treating MS: 9 (42.9 %) dimethyl fumarate, 5 (23.8 %) teriflunomide, 4 (19.0 %) interferonβ-1a and 3 (14.3 %) glatiramer acetate.

3.2. Anthropometric evaluation

BMI was significantly decreased from 24.7 ± 2.7 at T0 to 22.7 ± 2.5 at T1 ($p = 0.001$). Similarly, FM and FFM changed from 22.2 ± 6.6 to 18.0 ± 6.6 ($p = 0.009$) and from 49.1 ± 7.1 to 47.9 ± 6.6 ($p = 0.043$) after 6 months of KD, respectively.

3.3. Psychological status

Mean scores for each subscale of the DASS-21 significantly decreased after KD (see Table 2).

3.4. Quality of life

Although almost all the subscales improved at T1, we observed statistically significant differences in: role limitations-physical, emotional well-being, energy, cognitive function, overall quality of life, and change in health. Regarding the composite scores, only the MHC scores significantly increased after KD (see Table 2).

3.5. Sleep evaluation

The diet therapy improved all the sleep complaints (see Figs. 1 and 2). The number of MS patients affected by poor sleep was more than halved at the follow-up (T0: 14 versus T1: 5, $p = 0.012$), and the prevalence of EDS, that was 38.1 % before KD, decreased to 9.5 % after the treatment ($p = 0.031$).

As reported in Table 3, we found no significant correlations between sleep features and anthropometric measurements after KD. Poor sleep, as measured by the global PSQI score, was significantly correlated with symptoms of anxiety and stress, as measured by the DASS-21, and with mental and physical health, as measured by the MSQOL-54, at T1. Differently, a correlation of psychological status and QoL with EDS was not found.

Our multivariate linear regression models confirmed that the global PSQI score was an independent predictor of anxiety, stress, and mental health at T1. Differently, the association between poor sleep and PHC was lost after controlling for confounders (see Table 4).

Table 2
Psychological status and quality of life before (T0) and after (T1) ketogenic diet therapy.

	T0	T1	p
Mean DASS-21 scores			
Depression	5.7 ± 4.0	1.5 ± 2.1	0.001
Anxiety	4.3 ± 4.1	1.7 ± 2.7	0.003
Stress	9.9 ± 5.7	5.9 ± 5.7	0.001
Mean MSQOL-54 scores			
Physical function	78.3 ± 17.2	78.3 ± 17.3	1.000
Role limitations-physical	41.7 ± 38.9	70.9 ± 36.9	0.023
Role limitations-emotional	56.3 ± 43.6	71.4 ± 42.5	0.168
Pain	81.7 ± 58.6	77.1 ± 29.8	0.764
Emotional well-being	64.6 ± 24.9	74.9 ± 15.1	0.036
Energy	40.2 ± 22.5	53.7 ± 23.4	0.050
Health perception	48.3 ± 22.9	54.6 ± 20.5	0.337
Social function	64.7 ± 23.7	74.4 ± 12.8	0.124
Cognitive function	61.9 ± 23.4	83.4 ± 13.8	0.001
Health distress	73.6 ± 15.9	81.7 ± 7.1	0.069
Overall quality of life	57.4 ± 29.7	71.4 ± 18.7	0.050
Sexual function	69.0 ± 29.9	74.9 ± 32.7	0.495
Satisfaction with sexual function	48.8 ± 36.6	45.2 ± 45.1	0.769
Change in health	45.7 ± 30.4	69.0 ± 27.3	0.003
MHC	62.3 ± 20.1	75.5 ± 17.5	0.002
PHC	63.9 ± 17.2	70.9 ± 21.5	0.260

DASS-21: Depression Anxiety Stress Scale-21; MSQOL-54: Multiple Sclerosis Quality of Life-54; MHC: mental health composite; PHC: physical health composite.

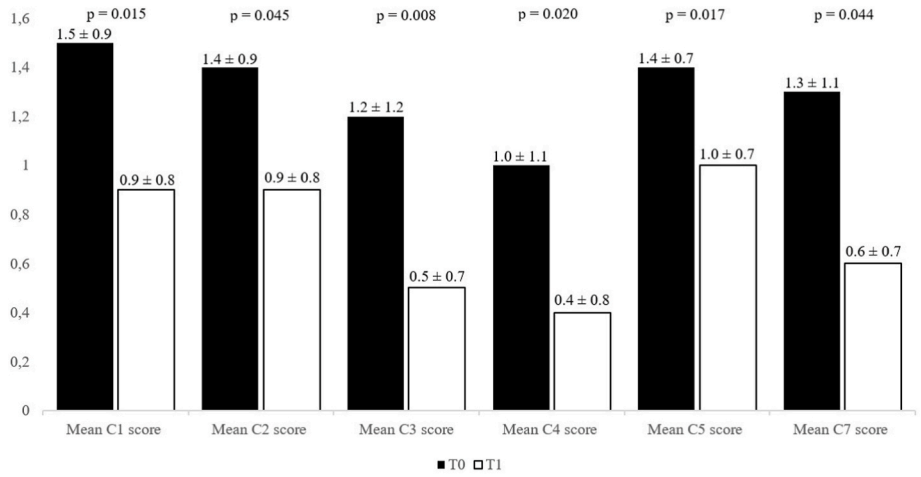

Fig. 1. Mean scores for each component of the Pittsburgh Sleep Quality Index before (T0) and after (T1) ketogenic diet therapy
C1 = sleep quality; C2 = sleep onset latency; C3 = sleep duration; C4 = sleep efficiency; C5 = sleep disturbance; C7 = daytime dysfunction.
Mean C6 scores, i.e. "Use of hypnotic drugs", are lacking because hypnotic drugs could not be used during the study period.

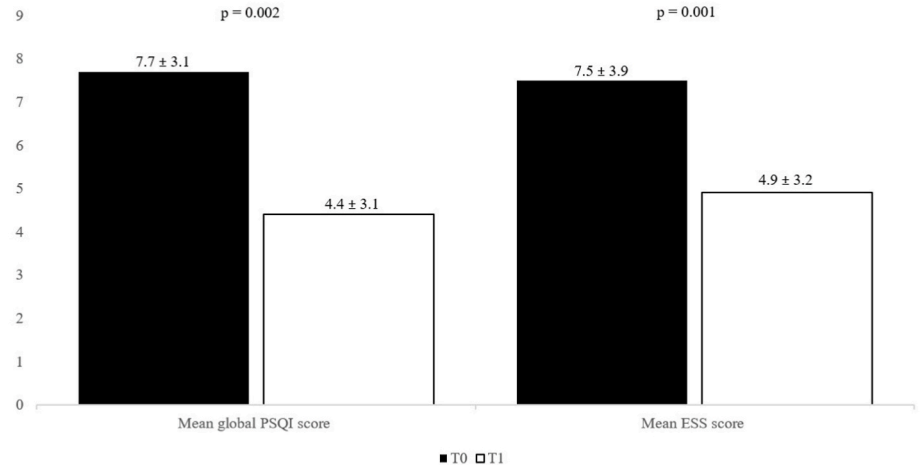

Fig. 2. Mean scores for the global Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scales before (T0) and after (T1) ketogenic diet therapy
PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale.

Table 3
Correlations of anthropometric measurements, psychological status, and quality of life with sleep features after ketogenic diet therapy.

	Global PSQI score	ESS score
BMI	r = −0.12, p = 0.734	r = 0.14, p = 0.697
FM	r = −0.12, p = 0.747	r = −0.04, p = 0.920
FFM	r = −0.33, p = 0.347	r = 0.48, p = 0.156
DASS-21 Depression	r = 0.12, p = 0.598	r = 0.05, p = 0.827
DASS-21 Anxiety	r = 0.67, p = 0.001	r = −0.13, p = 0.569
DASS-21 Stress	r = 0.69, p = 0.001	r = 0.04, p = 0.861
MSQOL-54 MHC	r = −0.62, p = 0.003	r = 0.24, p = 0.284
MSQOL-54 PHC	r = −0.46, p = 0.034	r = 0.19, p = 0.394

PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale; BMI = body mass index; FM = fat mass, FFM = fat-free mass; DASS-21: Depression Anxiety Stress Scale-21; MSQOL-54: Multiple Sclerosis Quality of Life-54; MHC: mental health composite; PHC: physical health composite.

4. Discussion

For the first time, we demonstrated that KD may improve subjective sleep quality and daytime somnolence in non-disabled or minimally disabled patients with relapsing-remitting MS. In addition, we observed that KD seems to have a positive impact on psychological status and QoL in these patients, but these results are largely due to an improved sleep quality.

Sleep complaints are very common in MS patients. A polysomnographic study revealed that 74 % of 66 consecutive MS patients were affected by sleep disorders [21]. The most common sleep complaints are as follows: insomnia, sleep-disordered breathing, circadian rhythm disorder, RLS, narcolepsy, and REM sleep behavior disorder. A recent review by Foschi et al. correlated the more common sleep disturbances in MS patients to the involvement of specific brain regions, analyzing their relationship with MRI findings [3]. Although this study raises the awareness of MS specialists regarding secondary sleep-related disorders in patients with moderate to severe disability and high lesion load, we still know too little about sleep and its features in MS subjects without or with minor impairment in the functional systems investigated by the EDSS. In our sample of non-disabled or minimally disabled MS patients, we observed a high prevalence of subjective sleep complaints. In particular, poor sleep quality affected more than half of the population, i.e. 66.7 %, while EDS was reported by 38.1 % of them. These findings are even more relevant, considering that we excluded subjects with OSA, RLS, and those affected by depressive and anxiety disorders. Further larger studies should confirm these preliminary results.

There is a growing interest in using specific diet regimens as a new therapeutic avenue for MS. A recent systematic review by Sanchez et al.

Table 4
Independent predictors of psychological status and quality of life after ketogenic diet therapy.

Variable	Standardized β value	p
DASS-21 Depression predictors ($R^2 = 0.12$; F = 1; p = 0.981)		
Age	0.12	0.877
Sex	0.17	0.739
MS duration	0.12	0.831
EDSS score	0.03	0.941
Global PSQI score	0.23	0.707
ESS score	−0.16	0.877
DASS-21 Anxiety predictors ($R^2 = 0.80$; F = 15; p = 0.030)		
Age	−0.54	0.168
Sex	−0.31	0.220
MS duration	−0.09	0.736
EDSS score	0.49	0.064
Global PSQI score	0.96	0.011
ESS score	0.18	0.406
DASS-21 Stress predictors ($R^2 = 0.65$; F = 75; p = 0.015)		
Age	−0.28	0.546
Sex	0.08	0.701
MS duration	−0.05	0.790
EDSS score	0.01	0.989
Global PSQI score	0.86	0.001
ESS score	0.05	0.809
MSQOL-54 MHC predictors ($R^2 = 0.85$; F = 72; p = 0.012)		
Age	0.61	0.086
Sex	0.41	0.080
MS duration	0.37	0.128
EDSS score	−0.18	0.400
Global PSQI score	−1.15	0.002
ESS score	−0.22	0.256
MSQOL-54 PHC predictors ($R^2 = 0.47$; F = 13; p = 0.482)		
Age	−0.51	0.407
Sex	−0.03	0.946
MS duration	0.18	0.765
EDSS score	−0.10	0.791
Global PSQI score	−0.14	0.767
ESS score	0.17	0.625

DASS-21: Depression Anxiety Stress Scale-21; MS = multiple sclerosis; EDSS: Expanded Disability Status Scale; PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale; MSQOL-54: Multiple Sclerosis Quality of Life-54; MHC: mental health composite; PHC: physical health composite.

suggests that diet can affect MS through the gut microbiota. Diet can directly affect the gut microbiota by providing substrates to support the growth of gut community members or by inhibiting the growth of other gut community members. In addition, diet can indirectly influence the gut microbiota by influencing host immunity, intestinal barrier function, and production of host-derived secondary products [22]. Regarding KD, it suppresses experimental autoimmune encephalomyelitis by reducing proinflammatory T helper 1 and T helper 17 responses, reducing reactive oxygen species production, and increasing the proportion of anti-inflammatory regulatory T cells [23,24]. Three open-label clinical trials of KD therapy for MS, including two randomized controlled trials (class II evidence) [23,25] and one single-arm pilot study (class IV evidence) [6], have been published since 2016. They reported beneficial effects of KD on several MS-related outcomes, including EDSS [6,23], QoL [23], depression [6], and anthropometric measures [6]. Unfortunately, no information on sleep was collected and analyzed. Our study demonstrates that KD can also improve sleep complaints in MS subjects. With respect to baseline, our patients, after 6 months of diet therapy, showed a significant improvement involving all the PSQI domains, i.e. sleep quality, sleep onset latency, sleep duration, sleep efficiency, sleep disturbance, and daytime dysfunction. Indeed, the prevalence of poor sleep quality decreased from 66.7 % to 23.8 %. Perhaps due to an improved sleep quality, EDS prevalence was reduced by 28.6 % after KD. To date, a limited number of studies, focused on patients affected by epilepsy and OSA, have been performed to investigate the effects of KD on sleep [26–29]. Recently, we observed that migraine patients improved their sleep complaints, i.e. insomnia, sleep quality, and EDS, after 3 months of KD therapy. Interestingly, sleep features modifications were not correlated with migraine improvements or anthropometric changes [7]. KD might improve sleep by increasing GABA production and enhancing slow-wave activity during NREM sleep [30,31]. In addition, KD might modulate sleep also by Brain-derived Neurotrophic Factor (BDNF) protein. It has been documented that KD increases levels of BDNF, which in turn improves sleep complaints [32].

The pilot study by Brenton et al. reported that depression scores, as measured by the Beck Depression Inventory, significantly improved after 6 months of KD in a sample of 65 patients affected by relapsing-remitting MS [6]. These results were confirmed by our sample of 21 MS patients investigated using the DASS-21. In addition to depression, also anxiety and stress symptoms were ameliorated after KD. After 6 months of diet therapy, a significant direct correlation between the global PSQI score and symptoms of anxiety and stress was observed. Since this relationship remained significant after controlling for several confounders in the multivariate analyses, KD seems to reduce anxiety and stress symptoms by improving sleep quality. Differently, daytime somnolence had no significant correlation with psychological status at T1.

A recent systematic review and network meta-analysis of randomized trials assessed the efficacy of different dietary approaches on MS-related QoL. Although limited by the low quality of the included trials, the authors concluded that dietary interventions may improve physical and mental QoL in MS [33]. Choi et al. randomized 60 patients affected by relapsing-remitting MS to: control diet (n = 20), fasting-mimicking diet for 7 days followed by a Mediterranean diet for 6 months (n = 20), and KD for 6 months (n = 20). The KD cohort displayed clinically meaningful improvements in the MSQOL-54 scales at 6 months [23]. A further study by Lee et al. did not confirm that KD is better than usual diet in improving QoL of MS patients [25]. In our sample, several subscales of the MSQOL-54 rose after KD. In particular, the domains related to mental health had the best response to diet therapy. These positive effects of KD on QoL were, almost partially, due to an improved sleep quality that represented an independent predictor of MHC in the multivariate analysis. This result is not surprising since we previously demonstrated that scores for each SF-36 domain, and the mental component summary and physical component summary scores were significantly lower in poor sleepers than in good sleepers among MS patients [5].

Finally, although out of scopes of this study, which included clinically stabled patients, we wonder if the amelioration of sleep quality obtained with KD might contribute to the positive immune changes observed by other studies after KD [6,23].

The results of this exploratory study are limited by the absence of a control group on a standard diet, the small sample size, and the assessment of sleep complaints based on self-reported scales, which does not permit the exclusion of a placebo effect. In addition, since we used a self-report tool for monitoring psychological status, it is possible that patients developing depressive or anxiety disorder in the time interval between T0 and T1 were not excluded from our sample. Although self-administered, the DASS-21 is a validated scale for the evaluation of psychological status. If it has not identified depression and anxiety at T0 and T1, the hypothetical development between the two assessments should have been of a kind auto-resolved before the second evaluation, which is unreliable.

In conclusion, we demonstrated that 6 months of KD therapy seems to improve sleep quality and daytime somnolence in non-disabled or minimally disabled patients with relapsing-remitting MS. KD may have a positive impact on psychological status and QoL of MS patients, mainly through improving sleep quality. Further, controlled studies with larger sample sizes are needed to confirm these preliminary results. In particular, future researches should objectively confirm our subjective sleep quality results at least employing simple sleep monitoring, such as wearable sleep-trackers.

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Informed consent

It was obtained from all patients or their representatives.

Ethical approval

The study conformed to the Declaration of Helsinki of the World Medical Association and was approved by the Comitato Etico Unico Regionale del Friuli Venezia Giulia (CEUR-2020-SPER-124).

Guarantor

G.M.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

Not applicable.

CRediT authorship contribution statement

Giovanni Merlino: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Riccardo Garbo:** Conceptualization, Methodology. **Simone Dal Bello:** Software, Resources. **Ilaria Del Negro:** Software, Resources. **Eleonora Lamon:** Software. **Francesca Filippi:** Investigation, Resources. **Andrea Bernardini:** Investigation. **Simone Lorenzut:** Investigation, Resources. **Laura Ceccarelli:** Investigation. **Arianna Cella:** Investigation. **Alessandro Marè:** Investigation. **Yan Tereshko:** Investigation. **Gian Luigi Gigli:** Validation, Visualization. **Mariarosaria Valente:** Validation, Supervision.

Declaration of competing interest

Authors declare none.

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