REVIEW

Role of Ketogenic Diets in Multiple Sclerosis and Related Animal Models: An Updated Review

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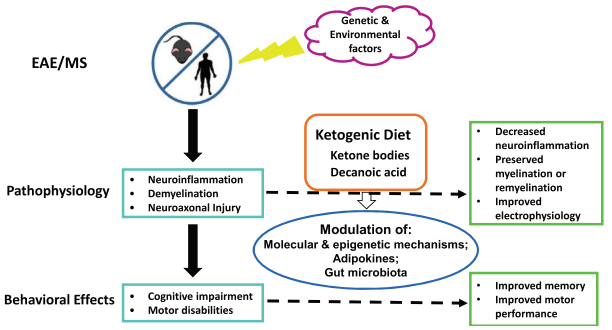
ABSTRACT

Prescribing a ketogenic diet (KD) is a century-old dietary intervention mainly used in the context of intractable epilepsy. The classic KD and its variants regained popularity in recent decades, and they are considered potentially beneficial in a variety of neurological conditions other than epilepsy. Many patients with multiple sclerosis (MS) have attempted diet modification for better control of their disease, although evidence thus far remains insufficient to recommend a specific diet for these patients. The results of 3 pilot clinical trials of KD therapy for MS, as well as several related studies, have been reported in recent years. The preliminary findings suggest that KD is safe, feasible, and potentially neuroprotective and disease-modifying for patients with MS. Research on corresponding rodent models has also lent support to the efficacy of KD in the prevention and treatment of experimental autoimmune encephalomyelitis and toxin-induced inflammatory demyelinating conditions in the brain. Furthermore, the animal studies have yielded mechanistic insights into the molecular mechanisms of KD action in relevant situations, paving the way for precision nutrition. Herein we review and synthesize recent advances and also identify unresolved issues, such as the roles of adipokines and gut microbiota, in this field. Hopefully this panoramic view of current understanding can inform future research directions and clinical practice with regard to KD in MS and related conditions. *Adv Nutr* 2022;13:2002–2014.

Statement of Significance: Existing studies concerning ketogenic dietary therapy for multiple sclerosis and relevant animal models have rarely been examined systematically. This narrative review updates and synthesizes preclinical and clinical evidence regarding the effects and mechanisms of action of ketogenic diets in these contexts.

GRAPHICAL ABSTRACT



Keywords: β-hydroxybutyrate, decanoic acid, demyelination, experimental autoimmune encephalomyelitis, ketogenic diet, multiple sclerosis, neuroinflammation

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Introduction

Multiple sclerosis (MS) is one of the major chronic inflammatory diseases of the central nervous system (CNS), affecting ∼2.3 million people worldwide (1). There is currently no cure for MS, and treatment remains unsatisfactory despite an increasing therapeutic armamentarium in recent decades. A substantial fraction of patients with MS expressed interest in and willingness for a trial of dietary therapy in the hope that it would ameliorate their disease (2). For instance, nearly two-thirds of the study subjects in a clinical trial of modified Atkins diet had already attempted dietary changes before they participated in that trial (3). The ketogenic diet (KD) and related dietary styles were preferred by many patients with MS. In a survey of dietary characteristics conducted in North America, these patients often adopted a low-carbohydrate, low-calorie, or Atkins diet in some periods of their disease course (4).

In contrast to the enthusiasm about diet modification on the patients' side, evidence supporting the use of any specific diet for MS was considered to be insufficient (5–7), and KD was often not specifically addressed in review articles examining the role of dietary intervention in MS (7, 8). It has been suggested that KD might exert anti-inflammatory and neuroprotective effects in patients with various neurological disorders (9–13), including progressive MS (14). However, KD is not without potential adverse effects, and the chronic low-grade metabolic acidosis associated with KD is a cause for concern. To prevent the acidosis, it has been suggested that dietary protein, which is a source of endogenous acidic metabolites, is maintained at the level of 1–2 g/kg/d, and consumption of alkaline mineral–rich green vegetables is maximized (15). Moreover, it appears that the effects of KD on the CNS are context dependent, and KD could be detrimental in some situations. For instance, KD aggravates cognitive impairment induced by intermittent hypoxia in mice (16). This negative cognitive impact is mediated by the expansion of IFN-γ–producing T helper 1 (Th1) cells, and Th1 polarization is also implicated in the pathogenesis of experimental autoimmune encephalomyelitis (EAE) and MS (17). Nonetheless, KD has shown promise in various rodent models of dysmyelination or demyelination. In a mouse model of Pelizaeus–Merzbacher disease (a kind of inherited leukodystrophy), a KD rescued the myelination defect and clinical phenotype (18). In EAE and cuprizone-induced demyelination mouse models, KD also ameliorated disease activity in terms of neuropathology and behaviors (19, 20). Several pilot clinical trials concerning the effects of KD on patients with MS have been carried out in recent years (3, 17, 21). Therefore, this is a prime time to re-evaluate the role of KD in MS and its corresponding animal models, and to identify knowledge gaps that deserve further research.

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Abbreviations used: ASIC, acid-sensing ion channel; BHB, β-hydroxybutyrate; CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; EDSS, Expanded Disability Status Scale; FMD, fasting mimicking diet; FOXO, forkhead box class O; HDAC, histone deacetylase; KD, ketogenic diet; MCT, medium-chain triglyceride; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NLRP3, NOD-, LRR-, and pyrin domain–containing protein 3; PBMC, peripheral blood mononuclear cell; PPARγ, peroxisome proliferator-activated receptor γ; SIRT1, sirtuin 1; Th, T helper cell; VGLUT, vesicular glutamate transporter.

The Effects of KD on MS (Human Studies)

A PubMed search using the search terms "ketogenic diet" AND ("multiple sclerosis" OR "experimental autoimmune encephalomyelitis") was performed to identify relevant publications. The last search date was December 31, 2021.

Study design and execution

Three open-label clinical trials of KD therapy for MS, including 2 randomized controlled trials (class II evidence) (17, 21) and 1 single-arm pilot study (class IV evidence) (3), have been published since 2016. There were also other research articles focusing on certain aspects of KD effects in patients with MS, including the ramifications of the clinical trial conducted by Bock et al. (clinicaltrials.gov identifier: NCT01538355) (22–24). In addition, a single case report was identified (25). An overview of these studies is presented in **Table 1**.

KD regimens used in these studies were heterogeneous, including variants such as a modified Atkins diet (3) and medium-chain triglyceride (MCT)–based KD modified from the Wahls Paleo Diet (21). The latter was considered to be the KD version of the modified Paleolithic diet. The ketogenic ratio (i.e., the ratio of grams of fat to grams of carbohydrate and protein combined) of study diets, either reported in the articles or calculated from the diet descriptions, ranged from 1 to 2.2 across studies (17, 21, 25) and was lower than that of the classic KD (with a ketogenic ratio $\leq$4) (26). The exception was the study published by Benlloch et al. (27), in which the ketogenic ratio was far below 1. An isocaloric KD was originally claimed as the study diet in their article, but the carbohydrate content (40%) and the degree of ketosis achieved [mean serum β-hydroxybutyrate (BHB) = 0.10 mmol/L] did not conform to KD in the general sense. Therefore, the study could not be considered a genuine KD study. Indeed, the authors admitted later that their study diet would be more appropriately termed a "coconut oil-enriched Mediterranean diet" (28).

The classic KD and MCT diet often result in different levels of nutritional ketosis, even when the ketogenic ratio is the same. They also exhibited differential clinical effects in a mouse model of hypomyelinating disease (18). Therefore, caution should be exercised in comparing and interpreting research results because different KD regimens were used across studies. Another issue that deserves attention is the differences in the calorie content of study diets. In the case study using KD as the sole therapy for secondary progressive MS, the dietary regimen was actually a combination of KD and a calorie-restricted (i.e., 75% of the recommended

TABLE 1 Overview of studies evaluating a ketogenic diet in patients with MS: study design and execution[1]

Author (year)	Study design	Dietary interventions	Supervision or coaching	Study participants	Age of study subjects, y	Other notes or comments
Choi et al. (2016) (17)	Randomized, parallel-group, 3-arm trial	Experimental groups: KD for 6 mo, or a single cycle of a modified FMD for 7 d followed by a Mediterranean diet for 6 mo. Comparator group: control diet	Nutritional coach during group-based workshops on 3 weekends	60 RRMS (20 for each group; 18/18/12 in KD/FMD/control group completed study, respectively)	Adults, mean 41.3 ± 8.2	clinicaltrials.gov identifier: NCT01538355
Swidsinski et al. (2017) (24)	Interventional study (focusing on microbiome study)	KD for 6 mo	Nutritional coach during group-based workshops on 3 weekends	10 RRMS, 14 HC	Adults, details not reported	Longitudinal evaluation of colonic microbiome change under KD, without evaluation of clinical effects; HC group was not treated with KD, so the effects of KD on MS vs. HC could not be compared
Bock et al. (2018) (22)	Randomized, 3-arm trial	Experimental groups: adapted (by Dr Bock) KD for 6 mo, or FMD (7-d fasting followed by usual diet). Comparator group: control diet	Nutritional coach	24 RRMS (11 on adapted KD, 5 on FMD, 8 controls)	Adults, mean 43.1 ± 8.8	Adapted KD and CR groups were pooled for analysis due to small sample size (because of patients' dropout and loss of blood samples)
Nathan et al. (2019) (25)	Single case study	KD plus CR (75%). Ketogenic ratio 2.2	Diet diary, daily urine ketones	1 SPMS	60	KD as monotherapy for SPMS
Benlloch et al. (2019) (27)	Prospective, mixed and quasi-experimental pilot study	Isocaloric, MCT-rich diet for 4 mo	Weekly telephone calls in which patients were asked about any problems in following the diet	20 RRMS, 6 SPMS, 1 PPMS	Adults, mean 44.56 ± 11.27	Not genuinely ketogenic (see text for details)
Brenton et al. (2019) (3)	Single-arm, open-label pilot study	Modified Atkins diet for 6 mo	The study dietitian provided a personalized educational session on initiation and maintenance of MAD, and provided contact information so that subjects could use her as a resource outside of study visits	20 RRMS	15–50	Study subjects largely overweight or obese; no comparator group

(*Continued*)

TABLE 1 (*Continued*)

Author (year)	Study design	Dietary interventions	Supervision or coaching	Study participants	Age of study subjects, y	Other notes or comments
Lee et al. (2021) (21)	Randomized, waitlist controlled, open-label study	Experimental groups: MCT-based KD for 12 wk, or modified Paleolithic diet. Comparator group: usual diet. Ketogenic ratio 0.99 ± 0.47	Participants were taught the study diet by RD, who answered all diet-related questions throughout the study. RD made nutrition counseling calls to participants 2–3 d after visit 1, then weekly for 3 wk	10 SPMS, 2 PPMS, 1 PRMS, 1 RRMS; 5 on MCT-based KD, 6 on modified Paleolithic diet, 4 on usual diet	36–63	clinicaltrials.gov identifier: NCT01915433
Bock et al. (2022) (23)	Retrospective evaluation of a randomized, 3-arm trial	As described in the study of Bock et al. (2018) (22) (see above)	As described in the study of Bock et al. (2018) (22) (see above)	40 RRMS (17 on adapted KD, 14 on FMD, 9 controls)	Adults, mean 43.06 ± 9.7	

[1]CR, calorie restriction; FMD, fasting mimicking diet; HC, healthy controls; KD, ketogenic diet; MAD, modified Atkins diet; MCT, medium-chain triglyceride; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; PRMS, progressive relapsing multiple sclerosis; RD, registered dietitian; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

calorie intake) diet (25). It might be difficult to tease out the effects of KD from those of calorie restriction in this case, because intermittent calorie restriction per se might exert beneficial effects in patients with MS in the absence of significant changes in BHB concentration (29). One study made a head-to-head comparison between KD and a fasting mimicking diet (FMD) in this context (17). The results suggest that both dietary regimens are safe and feasible for patients with MS, whereas FMD leads to more significant improvement in overall quality of life, physical health, and mental health compared with KD. However, it might be difficult to determine whether the improvements seen in the FMD group can be attributed to the 7-d FMD per se or the 6-mo Mediterranean diet that followed. An ongoing study (clinicaltrials.gov identifier: NCT03508414) aims to compare KD and FMD regarding their intermediate-term (18-mo) efficacy, using change in lesion load on T2-weighted MRI of the brain as the primary outcome measure (30).

Most studies included a nutritional coach or dietitian for diet-related instruction and/or counseling during the implementation of dietary therapy (3, 17, 21, 22, 24). This was not specifically mentioned in 2 studies (25, 27). The adherence to therapeutic diet was generally assessed using food diary, urine ketones, and blood ketones measurements (3, 21, 23, 25), and the latter were also used to ensure that nutritional ketosis was achieved.

Study findings and implications

Most studies reported beneficial effects of KD on some aspects of MS-related outcomes (**Table 2**), including Expanded Disability Status Scale (EDSS) score (3, 17, 25), health-related quality of life (17), fatigue (3), depression (3), and anthropometric measures such as body weight, BMI, and/or total fat mass (3, 25). Two studies reported favorable effects of KD on biomarkers of glucose homeostasis (3, 21), whereas 1 study reported no significant effect in this regard (22). One study reported a significant decrease of leptin after a 3-mo period of KD (3), which is consistent with the KD-induced changes in anthropometric measures. One study found that serum neurofilament light chain, a marker of neuroaxonal damage, decreased significantly in patients treated with KD (23). By comparison, reduction of serum neurofilament light chain was not observed in patients treated with FMD or common diet. It is also notable that the temporal pattern of serum neurofilament light chain concentration was not linear in patients treated with KD, and significant reduction of this biomarker was only observed after 6-mo dietary therapy, suggesting relatively late onset of KD's neuroprotective effects. Among the KD-treated patients in the 3 clinical trials, only 1 patient experienced a clinical relapse during the study period (17); other patients did not exhibit overt disease progression. However, the clinical course of MS is usually insidious, hence further studies with a longer duration of follow-up could be needed to determine if a KD is effective in reducing disease relapse or progression.

The patient characteristics varied markedly between studies. For example, patients in the clinical trial conducted by

TABLE 2 Overview of studies evaluating a ketogenic diet in patients with MS: the results[1]

Author (year)	EDSS score	Quality of life	Fatigue	Depression	Anthropometric measures	Biomarkers	Other findings or comments
Choi et al. (2016) (17)	Mildly yet significantly improved at 3 and 6 mo	Clinically meaningful improvement in MSQOL-54 at 3 mo	Not reported (assessed using MFIS)[2]	Not reported (assessed using BDI)[2]	Not reported[2]	Slight reduction in lymphocyte and WBC counts	■ High compliance rate (90%) ■ Adverse events (KD/FMD/control group): respiratory tract infection (n = 12/7/9), diarrhea (n = 3/0/3), headache (n = 2/2/0), nausea (n = 2/0/0), ureteric colic (n = 1/0/0), urinary tract infection (n = 1/2/1) ■ One relapse in KD group during 6-mo study period (4 in control diet group, 3 in FMD group)
Swidsinski et al. (2017) (24)	Not reported	Not reported	Not reported	Not reported	Not reported	Dynamic changes in colonic microbiome	The effects of KD on colonic microbiome were biphasic. Bacterial concentrations and diversity were further reduced from baseline initially, then they started to recover at week 12
Bock et al. (2018) (22)	Expression of all target genes showed statistically nonsignificant trend for positive correlation with the EDSS score	ALOX5 and COX1 expression were inversely correlated with MSQOL-54 at 6 mo	Not reported	Not reported	Improved BMI (P = 0.008)	No significant effects on fasting blood sugar and insulin	■ Target genes in this study were those coding for biosynthetic enzymes for proinflammatory (ALOX5, COX1, COX2) and anti-inflammatory (ALOX15) eicosanoids ■ Significant increase in serum BHB (mean 1.44 mmol/L)
Nathan et al. (2019) (25)	EDSS score deterioration (6.0 → 7.5) after stopping KD, and improving after resumption of KD	No formal assessment was reported	Not reported	Not reported	BW decreased from 67.1 to 65 kg and maintained (= his ideal BW)	CSF-specific OCBs remained positive	Disease activity (EDSS) apparently correlated with use/discontinuation/ resumption of KD

(*Continued*)

TABLE 2 (*Continued*)

Author (year)	EDSS score	Quality of life	Fatigue	Depression	Anthropometric measures	Biomarkers	Other findings or comments
Benlloch et al. (2019) (27)	Not reported	Not reported	Not reported	Not reported	Significant increase in lean mass and decrease in fat mass	■ Ghrelin: no significant change ■ Paraoxonase 1 (an antioxidant marker): significant increase	■ Significant satiating effect (decreased hunger perception) ■ Significant yet modest increase in serum BHB (mean 0.10 mmol/L after the 4-mo intervention)
Brenton et al. (2019) (3)	Significant decrease in EDSS score at 6 mo	Not reported	Patient-reported fatigue (MFIS) improved ($P = 0.002$)	Patient-reported depression scores (BDI) improved ($P = 0.003$)	Reductions in BMI and total fat mass ($P < 0.0001$)	■ Leptin: significantly lower at 3 mo ($P < 0.0001$) ■ Adiponectin: no significant change ■ Insulin and hemoglobin A1c: significantly decreased	■ Adherence rate: 95% at 3 mo and 75% at 6 mo ■ Reported side effects included intermittent constipation ($n = 5$, 25%), menstrual irregularities ($n = 4$, 20%), and diarrhea ($n = 3$, 15%) ■ No new lesion on brain MRI at 6 mo
Lee et al. (2021) (21)	No clinically significant change	No significant change in MSQOL-54	No significant change in perceived fatigue (MFIS)	Not reported	Not reported[2]	Reduction in fasting blood sugar and insulin	Maximal mean plasma BHB was 1.48 ± 1.10 mmol/L (at 4 wk); ketosis was maintained (>0.5 mmol/L) at 8 and 12 wk
Bock et al. (2022) (23)	Not reported[2]	Not reported	Not reported	Not reported	Not reported[2]	Significant reduction in sNfL at 6 mo	■ One relapse in KD group during study period (3 in control diet group, 2 in FMD group) ■ A single cycle of FMD (7-d fasting) did not affect sNfL

[1] ALOX, arachidonate lipoxygenase; BDI, Beck Depression Inventory; BHB, β-hydroxybutyrate; BW, body weight; COX, cyclooxygenase; CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; FMD, fasting mimicking diet; KD, ketogenic diet; MFIS, Modified Fatigue Impact Scale; MSQOL-54, Multiple Sclerosis Quality of Life-54 questionnaire; OCB, oligoclonal band; sNfL, serum neurofilament light chain; WBC, white blood cell.
[2] Only baseline data were reported.

Lee et al. (21) were much more severe in terms of their EDSS score (≥4.5, as imposed by the inclusion criteria) compared with patients in Brenton et al.'s study (EDSS score 1.0–4.0) (3). In another study, the EDSS score of study subjects was not reported (27). Most studies recruited mainly patients with relapsing-remitting MS, whereas a clinical trial and a case report focused more on the effects of KD in progressive MS (21, 25). The age distribution of enrolled patients also differed between studies (Table 1), and pediatric MS has been underrepresented in existing studies. It appeared that younger patients with milder disease or a relapsing-remitting form of the disease benefited more from KD in terms of EDSS score, quality of life, and fatigue (Table 2), although further studies are clearly needed to identify the patient characteristics that lead to more favorable responses to KD intervention.

Adverse events were reported in 2 clinical trials (3, 17). The most common adverse events in KD-treated patients were respiratory tract infection [∼67% compared with 75% in control group (17)], gastrointestinal symptoms (diarrhea, constipation, nausea; 28 to 40%), and genitourinary problems (ureteric colic, urinary tract infection, menstrual irregularities; 11 to 20%). Serious adverse events were rarely encountered.

The role of gut microbiota

Gut microbiota and their metabolites are considered important players in mediating the immunological effects of dietary intervention (31). *Bifidobacterium* could induce intestinal Th17 cells (32), and the latter are implicated in the pathogenesis of CNS autoimmunity (33). KD has been associated with decreased abundance of *Bifidobacterium* in patients with obesity, which in turn results in decreased intestinal Th17 cells (34). Together, these findings suggest that KD can ameliorate MS through its microbiome-modulating effects. However, only 1 study to date reported the effects of KD on the gut microbiota of patients with MS (24). Swidsinski et al. (24) found that the overall mass and diversity of the colonic microbiome were reduced prior to KD intervention in these patients at the group level, although interindividual differences were evident. The effects of KD appeared to be dynamic during the 6-mo period of dietary intervention in these patients. The overall bacterial concentrations and diversity were further reduced initially (at ∼2 wk after the introduction of KD), then subsequently gradually recovered. An exception to this general trend was *Akkermansia*, which increased initially but declined later. *Akkermansia* has been implicated in mediating the antiseizure effect associated with KD (35). Furthermore, *Akkermansia* was found to be increased in patients with MS in a recent study, and the *Akkermansia* isolated from these patients ameliorated EAE in a mouse model (36). Taken together, these findings are broadly consistent and suggest a neuroprotective role of *Akkermansia* in MS and related conditions. The dynamic changes in gut microbiota, as reported by Swidsinski et al. (24), underscore the importance of longitudinal evaluation after dietary intervention. A caveat of their study was that the authors did not examine the associations between microbiome changes and clinical or paraclinical characteristics. More studies are needed to elucidate the reproducibility of their findings and the clinical significance of KD–microbiota interactions.

Limitations

The research literature reviewed has some limitations. First, these studies are largely pilot ones and exploratory in nature. The sample size is likely insufficient for clarification of KD's effects on many MS-related outcomes. In the study protocol of a 3-armed randomized controlled trial (NCT03508414) designed to compare KD and intermittent fasting, it was estimated that 111 patients needed to be enrolled to achieve a statistical power of 80%, assuming that the dropout rate is 10% (30). Adequate sample size is also required to assess potential effect modifiers. However, this is often practically difficult, as illustrated by a change of inclusion criteria due to low initial enrollment in a recent study (21). Second, the duration of treatment and follow-up was relatively short. Therefore, the impact of dietary intervention on relapse rate and long-term trajectory of disability accrual could not be assessed. Third, the ketogenic ratio of study diets was 2.2 or lower. It remains unclear whether a higher ketogenic ratio, as used in some studies of refractory epilepsy (26, 37), could bring about more therapeutic benefits in patients with MS. In addition, KD is considered particularly suitable for children with drug-resistant epilepsy because children have better dietary compliance and more efficient extraction and utilization of blood ketones (38). However, pediatric MS has been underrepresented in existing studies (Table 1), thus further research is needed to assess the role of KD in this patient population. Fourth, it has been recognized that changes in dietary macronutrient composition could rapidly alter the human gut microbiome (39), which in turn impacts health and diseases. However, KD–microbiota interaction in the context of MS was only addressed in 1 study (as reviewed above), and clinical correlations were not examined. Hopefully this issue is acknowledged and incorporated into future studies, as exemplified by an ongoing trial that listed gut microbiome change as a secondary end point (30).

The Effects of KD on EAE and Other CNS Demyelination Animal Models

Observational and interventional studies in human patients provide invaluable information regarding the safety, efficacy, and feasibility of KD in the treatment of MS. However, given the presence of multiple potential confounders, it has been relatively difficult to gain mechanistic understanding of dietary intervention from human studies. Animal research could play a complementary role in this regard. Several well-established animal models have been used to investigate the effects of KD on CNS demyelination. These models differ by their pathogenetic mechanisms and only recapitulate MS in some aspects. In short, the demyelinating process is immune-mediated in EAE models, whereas it is toxin-induced in cuprizone models (40). EAE is often viewed

as the corresponding animal model of MS, and multiple versions of EAE have been developed (41). In the studies reviewed below, EAE was induced by myelin oligodendrocyte glycoprotein $(MOG)_{35–55}$ in C57BL/6J (B6) mice. The resulting disease course was monophasic (42), in contrast to the relapsing-remitting course in the majority of patients with MS. Nonetheless, the neuropathological and immunological features of this model could mimic aspects of human MS, making it useful in dissecting the mechanisms of potential therapeutic interventions.

Table 3 summarizes the animal studies investigating the effects of KD on CNS demyelination models. Two studies examined the effects of KD, with different timing of initiation, in a $MOG_{35–55}$-induced EAE mouse model. Choi et al. (17) compared the therapeutic effects of various dietary regimens. KD attenuated disease severity when initiated around the onset of EAE. However, the effect was modest compared with that of FMD. In the other study, Kim et al. (19) studied the effects of KD initiated 7 d prior to the induction of EAE (i.e., ∼2–3 wk before clinical onset of EAE). It is worth noting that spatial memory deficits in EAE manifest prior to the onset of motor disability, which is reminiscent of the early appearance of cognitive dysfunction in pediatric MS before motor handicap ensues (43). This temporal sequence allows behavioral memory testing to be performed in EAE mice without the interference of suboptimal motor performance (19). The authors found that KD-treated mice exhibited improved learning and memory and also motor performance. The pathological effects at structural and electrophysiological levels were also rescued. Together these studies suggest that both preemptive (19) and therapeutic (17) use of KD is effective in ameliorating disease activity in EAE.

Two related studies examined the effects of KD in a cuprizone-induced demyelination mouse model in corpus callosum and hippocampus, respectively (20, 44). Both studies, with somewhat different KD regimens, reported beneficial effects of KD on neuropathological changes, including less demyelination, enhanced oligodendrocyte maturation, and reduced reactive astrocytes and microglia activation as compared with those treated with normal diet. Behavioral phenotyping showed that mice cotreated with KD exhibited better learning and memory, emotion, and motor performance than those treated with cuprizone alone. Consistent with that observed in an EAE model (17), KD also ameliorated cuprizone-induced body weight loss.

Excessive expression of proinflammatory cytokines and chemokines in the CNS and periphery, as well as the production of reactive oxygen species, were observed in EAE mice. These were largely suppressed when KD was instituted before EAE induction (19). Qualitatively similar results were also seen in cuprizone-induced demyelination models, in which KD-treated mice had decreased expression of proinflammatory cytokines (IL-1β, TNF-α), chemokine (CXCL 10), and oxidative stress marker (malondialdehyde) (20, 44). These data were also broadly consistent with findings from patients with MS, in whom KD attenuated the mRNA expression of proinflammatory cyclooxygenase and lipoxygenase (22). Taken together, human and animal research findings suggest that the beneficial effects of KD in MS/EAE can be attributed in part to its anti-inflammatory and redox modulatory properties.

Potential Molecular Links between KD and MS/EAE

The study of KD therapy for MS/EAE to date, as reviewed above, not only suggests a promising way of dietary intervention but also yields potential mechanistic insights in relevant contexts (**Figure 1**). It has been increasingly recognized that the ketone body species can play dual roles. They can be transported into neurons and converted to acetyl-CoA in the mitochondria, thereby serving as energy substrates. On the other hand, the ketone bodies and related metabolites, such as decanoic acid, can also act as signaling molecules (9, 11, 45). The following is a concise review of current evidence regarding several candidate molecular players implicated in mediating the effects of KD on MS/EAE.

Histone deacetylases

Histone deacetylase 3 (HDAC3), a member of class I HDACs, is involved in regulating inflammatory responses through deacetylase activity-dependent and -independent mechanisms (46). Its mRNA is expressed in significantly higher amounts in the peripheral blood mononuclear cells (PBMCs) of patients with MS (47), and it appears to be causally linked to IL-33 overexpression in these patients (48). Class I HDAC inhibition attenuates LPS-induced IL-33 expression in PBMCs derived from patients with MS (48). BHB inhibits HDAC3 in a dose-dependent manner (49), and KD ameliorates the increase in HDAC3 protein expression in the corpus callosum in a cuprizone-induced demyelination mouse model (20). HDAC1 is also involved in the pathogenesis of EAE (50), and it could also be inhibited by BHB (49).

On the other hand, sirtuin 1 (SIRT1), a member of class III HDACs, appears to have neuroprotective roles in MS and EAE (51, 52). KD is associated with enhanced SIRT1 expression in various cell types in the CNS, as well as better neurological outcomes in a cuprizone-induced demyelination mouse model (44). Taken together, these findings suggest that class I HDAC inhibition and/or SIRT1 augmentation could be potential mechanism(s) underlying the effects of KD on MS/EAE.

Acid-sensing ion channel

Acid-sensing ion channel (ASIC) subunit 1, encoded by the *ASIC1* gene, is overexpressed in both acute and chronic MS lesions (53). The acidosis in the spinal cord of EAE mice is sufficient to activate ASIC1. Both genetic ablation and pharmacological blockade of ASIC1 attenuate disease activity in EAE mice (54). A pilot study showed radiological evidence of a neuroprotective effect of amiloride, an ASIC1 blocker, in a cohort of primary progressive MS patients (53). The main ketone body species, namely BHB, acetoacetate, and acetone,

TABLE 3 Overview of studies evaluating the effects of a ketogenic diet in experimental demyelination models[1]

Author (year)	Animal model and KD regimen (ketogenic ratio)	Neuropathology or morphology	Motor function	Learning/memory (behavioral paradigm)	Anxiety/ depression	Body weight	Biomarkers	Other findings or comments
Kim et al. (2012) (19)	MOG_{35-55}-induced EAE mouse model; KD (6.3:1) started 7 d before EAE induction and continued until the time of killing	Reduced lesion volumes on T2-weighted imaging and preserved hippocampal volume on MRI	Decreased motor disability in nadir and recovery stage (motor scale)	Sustained preservation of spatial learning and memory (MWM)	Not reported	Not reported	Reduced brain ROS (in vivo bioluminescence imaging); reduced expression of cytokines (IL-1β, IL-6, TNF-α, IL-12, IL-17) and chemokines (IFN-γ, MCP1, MIP-1α, MIP-1β) in CNS and periphery	Sustained preservation of hippocampal LTP
Choi et al. (2016) (17)	MOG_{35-55}-induced EAE mouse model; KD (6.36:1) initiated at initial signs of EAE[2] and continued for 30 d	Not reported	Decreased motor disability (motor scale)	Not reported	Not reported	KD ameliorated body weight loss associated with EAE	Not reported	Compared with FMD, KD had more modest effects in ameliorating EAE symptoms. FMD reversed EAE progression in some mice, whereas KD did not
Zhang et al. (2020) (20)	CPZ-induced demyelination mouse model; normal diet vs. KD (1.21:1) concurrent with CPZ for 5 wk	Demyelination↓; promoted oligodendrocyte maturation (inferred by enhanced Olig2 protein expression); decreased reactive astrocytes and microglia activation	Not reported	Not reported	↓Anxiety-like behavior, ↑exploratory behavior (open field)	KD ameliorated CPZ-induced body weight loss	↓IL-1β, TNF-α, CXCL10 expression; ↑IL-10 expression; ↓expression of HDAC3 and NLRP3	Focus on corpus callosum; blood glucose concentrations significantly decreased in KD-fed mice
Liu et al. (2020) (44)	CPZ-induced demyelination mouse model; normal diet vs. KD (3.060:1) concurrent with CPZ for 5 wk	KD inhibited the activation of microglia (especially M1-like microglia) and reactive astrocytes, and enhanced the expression of mature oligodendrocytes; demyelination↓	↑Motor coordination (rotarod)	↓Learning/memory deficits (MWM)	↓Anxiety-like behavior; ↑exploratory behavior (open field)	KD ameliorated CPZ-induced body weight loss	Attenuated oxidative stress (MDA↓; GSH↑); enhanced expression of PPAR-γ and SIRT1/phospho-Akt/mTOR	Focus on hippocampus; blood glucose did not differ among the groups

[1] Akt/mTOR, protein kinase B/mammalian target of rapamycin; CNS, central nervous system; CPZ, cuprizone; CXCL, cysteine-X-cysteine motif chemokine ligand; EAE, experimental autoimmune encephalomyelitis; FMD, fasting mimicking diet; GSH, glutathione; HDAC, histone deacetylase; KD, ketogenic diet; LTP, long-term potentiation; MCP, monocyte chemoattractant protein; MDA, malondialdehyde; MIP, macrophage inflammatory protein; MOG, myelin oligodendrocyte glycoprotein; MWM, Morris water maze; NLRP3, nod-like receptor pyrin domain containing 3; Olig2, oligodendrocyte transcription factor 2; PPAR-γ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; SIRT1, sirtuin 1.
[2] Initial signs at ~8–14 d after immunization.

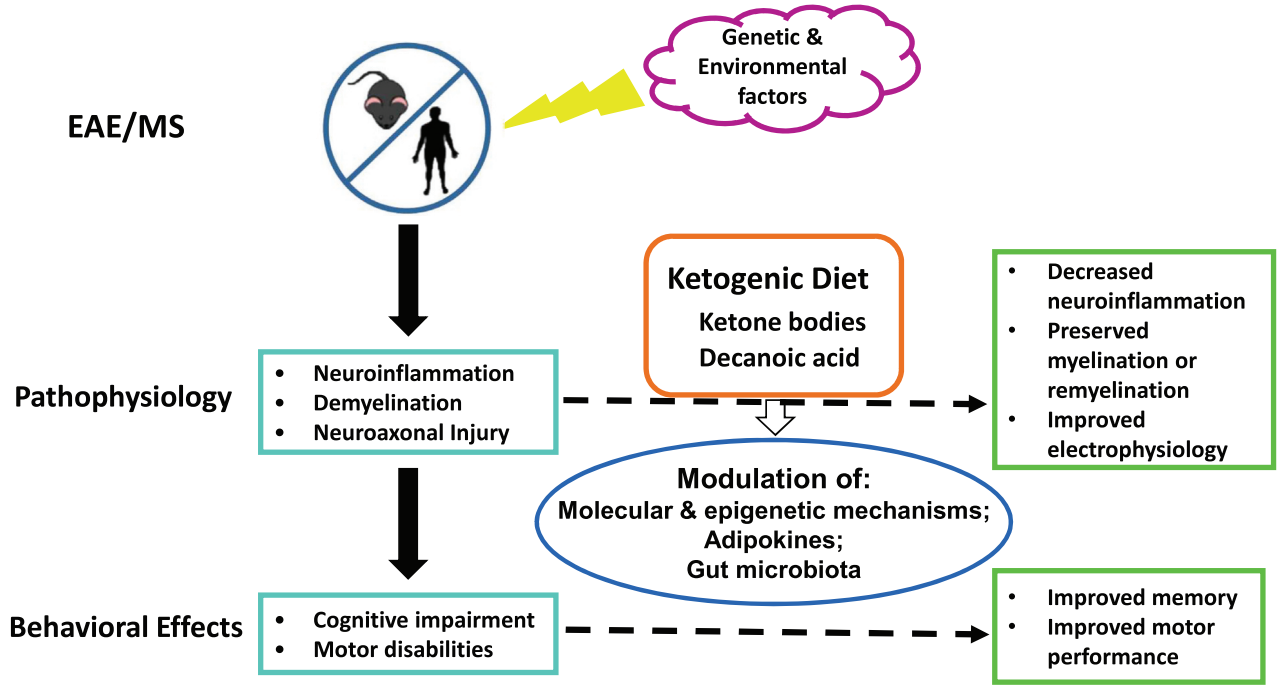

FIGURE 1 A graphical summary of effects of a ketogenic diet in patients with MS and animal models of MS. MS is a multifactorial condition involving both genetic and environmental factors. Diet is 1 of the modifiable risk or protective factors. Specifically, the ketogenic diet could ameliorate neuroinflammation, demyelination, and their attendant behavioral effects in MS and related conditions, presumably through a variety of epigenetic and other molecular mechanisms, modulation of adipokines, and alterations of gut microbiota. EAE, experimental autoimmune encephalomyelitis; MS, multiple sclerosis.

could inhibit ASIC-mediated currents in rat hippocampal neurons (55). Therefore, ASIC blockade might contribute to the beneficial effects of KD in patients with MS.

Forkhead box class O family

Members of the forkhead box class O (FOXO) gene family, *FOXO1* and *FOXO3A* in particular, are implicated in the genetic susceptibility of relapsing-remitting MS (56). BHB upregulates the expression of *Foxo1* (57) and *Foxo3a* (49) via histone β-hydroxybutyrylation and acetylation, respectively. Furthermore, FoxO1 is involved in oligodendrocyte regeneration and CNS myelination (58, 59), and FOXO3A contributes to oxidative stress resistance (49, 60). Taken together, members of the FOXO family could also be downstream mediators of KD in the context of MS/EAE.

Vesicular glutamate transporters

Vesicular glutamate transporter 1 (VGLUT1), encoded by the *SLC17A7* gene, is implicated in the remyelination process (61). Its expression was downregulated in a mouse model of progressive EAE (62). KD ameliorates age-related decline in VGLUT1 expression in rat hippocampus (63). Taken together, these findings suggest that VGLUT1 might be another potential molecular player mediating the effect of KD in the context of MS/EAE. Other VGLUTs might also be relevant. For example, a 6-fold increase in VGLUT2 expression has been observed in demyelinated lesions compared with the normal-appearing white matter in people with MS, and VGLUT2 expression is presumably linked to the remyelination process in this scenario (64). A recent study showed that KD resulted in a significant increase in the abundance of VGLUT2 (encoded by *Slc17a6*) in the hippocampus of rats with status epilepticus (65). On the other hand, it has been demonstrated that acetoacetate and BHB could inhibit glutamate transport through VGLUT2 in an in vitro system (66). Whether and how VGLUT2 is modulated by KD, as well as its consequences, remains to be investigated in the context of MS/EAE.

NOD-, LRR- and pyrin domain–containing protein 3 inflammasome

NOD-, LRR-, and pyrin domain–containing protein 3 (NLRP3) inflammasome, the most abundant inflammasome in the CNS, has been implicated in the pathogenesis of MS, EAE, and the cuprizone-induced demyelination model (67–69). KD ameliorates the increase in NLRP3 protein expression in the corpus callosum in the cuprizone-induced demyelination mouse model (20). Ketone body species, specifically BHB, can attenuate NLRP3 activation in vitro and in vivo in the brain (70, 71). These together suggest that KD might also exert a beneficial effect through modulation of innate immune mechanisms in people with MS.

Peroxisome proliferator-activated receptor γ

Markedly decreased expression of peroxisome proliferator-activated receptor γ (PPARγ) mRNA has been found in monocytes derived from patients with relapsing-remitting MS (72). PPARγ could suppress Th17 cell differentiation, and its downregulation has been associated with exacerbation of EAE (73). Activation of PPARγ in various cell types in the brain also contributes to remyelination, as well as protection from neuroinflammation and demyelination (74–76). Decanoic acid, a major component of the MCT-based KD, is a well-known PPARγ agonist (9, 77). KD is also associated with significantly increased PPARγ protein expression in hippocampus in a cuprizone-induced demyelination model (44). Taken together, these findings suggest that KDs, particularly those enriched in decanoic acid, might confer protection against neuroinflammation in part through enhanced PPARγ action.

Adipokines

Several adipokines, both proinflammatory (leptin, fatty acid binding protein-4) and anti-inflammatory (adiponectin), have been implicated in the regulation of disease activity in MS and EAE (73, 78–80). Indeed, an animal study suggested that adiponectin could ameliorate disease activity in EAE through enhanced SIRT1/PPARγ expression and suppression of Th17 cell differentiation (73). On the other hand, PPARγ agonism also induces adiponectin expression (81, 82), suggesting a bidirectional relation between PPARγ and adiponectin. KD has been associated with increased serum adiponectin concentration in human and rodent studies (83–85). Research into the effects of KD on fasting adipokines of patients with MS, however, was scarce. One study reported significantly decreased leptin and borderline increased adiponectin concentrations after a 3-mo period of KD in MS patients who were largely obese or overweight (3). More studies are clearly needed to elucidate the role of adipokines in dietary therapy for MS.

Conclusions

Nutritional care for MS has gained wide clinical and scientific interest among patients and clinicians. Thus far, the published studies on the effects of KDs on MS are either pilot clinical trials with small sample size or anecdotal reports. Nonetheless, their findings together showed that KD is feasible and well tolerated, and it exhibits neuroprotective and disease-modifying potential in this patient population. Similarly, investigations on the effects of KDs in the corresponding rodent models of CNS demyelination yielded promising results. It has also been better recognized that major metabolites in KDs, particularly BHB and decanoic acid, are not only energy substrates but also important signaling molecules in the context of neuroinflammation. Further research in this direction is needed to elucidate the mechanisms of action and to inform evidence-based clinical practice of KDs in MS and related conditions.

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