December 30, 2020

PharmacologyOnLine

Special issue • 2020 • vol.3 • 84-92

MULTIPLE SCLEROSIS AND KETOGENIC DIET: A STRATEGY SUPPLEMENTING CURRENT THERAPEUTIC APPROACHES

Massa Marida[1*], Morelli Silvana[2]

[1]Post Graduate University Course in "Diete e Terapie Nutrizionali Chetogeniche: Integratori e Nutraceutici (NutriKeto)" - Dipartimento di Farmacia, University of Salerno, Via Giovanni Paolo II – Fisciano (SA), Italy

[2]Ospedale Cotugno, Azienda Ospedaliera dei Colli Via Gaetano Quagliariello, 54, 80131 Napoli NA

Email address: marid.massa@gmail.com; nutriketo@unisa.it

Abstract

It has been known for centuries that the Ketogenic diet is a strict diet consisting of minimal carbohydrate and protein intake and increased fat intake and this nonpharmacologic mechanism may be used as co-adjuvant therapies for Multiple Sclerosis (MS). MS is an immune- mediated inflammatory neuronal disorder in which it is supposed a possible relationship between oxidative stress, mitochondrial dysfunction, glucose hypometabolism and inflammation. KD reduces oxidative stress by decreasing reactive oxygen species and increasing levels of antioxidant agents and it increases mitochondrial biogenesis offering an alternative to glucose as a source of fuel to the brain. Consequently KD leads to a reduction of inflammatory responses with structural and functional neuroprotective effects.

Keywords: *multiple sclerosis, ketogenic diet, ketone bodies, oxidative stress, mithocondrial dysfunction.*

Introduction

Many researchers haves established that about 2.5 million patients worldwide are affected by Multiple Sclerosis.

Infact, Multiple sclerosis (MS) is one of the most common immune-mediated inflammatory disorder of the central nervous system. It is a demyelinating disease in which the insulating covers of nerve cells in the brain and spinal cord are damaged. Disrupting the ability of parts of the nervous system to communicate, the results are physical, mental, and sometimes psychiatric problems. Specific symptoms can include diplopia, muscle spasms and weakness, numbness and mobility problems, cognitive disfunctions. MS has many forms: relapsing forms, the most common with new symptoms occurring in isolated attacks, or Progressive forms with symtoms worsen more steadily over time. The cause is unknown. However, the immune system play a role in the development of the disease.

There is at present no definitive therapy for progressive MS, although a few of the newer immunomodulatory agents may hold greater promise. A number of new treatments and diagnostic methods are under development. [1], and in this review, we will explore the evidence of neurodegeneration and the players in its pathogenesis that lead us to the potential of the ketogenic diet for use as co-adjuvant therapies for MS.

Methods

Relevant studies were identified by computerized searches on PubMed, and review of bibliographies of selected articles. We have used Multiple Sclerosis, ketogenic diet, neurological disease, low calorie diet as keywords. We included in the search reviews, meta-analysis, clinical trial, randomized controlled trials.

Results and Discussion

In the MS a dysregulated immune system attacks the central nervous system. Peripheral neuroantigen-specific T cells are activated and cross a compromised blood brain barrier (BBB) to enter the central nervous system and give rise to acute multifocal inflammatory lesions typical for MS. The activation of neuroantigen specific T cells is modulated by not fully understood genetic and enviromental factors. The BBB normally restrict access of immune cells to the brain and only T cells are able to pass. If, in an early stage of MS, neuroantigen specific T cells encounter their antigen presented by perivascular macrophages, they induce increased permeability of the BBB. This then allows other blood immune cells to infiltrate the CNS and complement microglial activation in the inflammatory response. [2]

Experimental autoimmune encephalomyelitis (EAE) is the most commonly used experimental model for MS. EAE is an animal model of brain inflammation, in which the interaction between immunopathological and neuropathological mechanisms leads to inflammation, demyelination, axonal loss and gliosis, a condition similar to MS. In a EAE model is observed that neutrophilis are one of the first leukocytes to arrive at the lesion site EAE and soon after, monocytes arrive.

Most infiltrating monocytes in EAE are of a proinflammatory lymphocyte antigen 6 complex $(Ly6C)^{hi}$ phenotype and are involved in demyelination at nodes of Ranvier. Moreover, they are the precursors of monocyte-derived dendritic cells and as such play an active role in the reactivation and polarization of T cells. [2]

Consequently an aberrant cytokine and chemokine burst characterized by T-cell proliferation may be a critical factor in the initiation of MS/EAE. Infacts, this inflammatory process leads to oligodendrocyte death, demyelination and axonal damage, which cause neurological damage.

The role of Reactive Oxygen Species in MS

An important role in the pathogenesis of MS is played by Reactive Oxygen Species (ROS). Oxidative stress results when production of ROS such as superoxide anion radicals, hydrogen peroxide, and hydroxyl radicals exceeds a biological system's ability to detoxify these reactive intermediates. ROS are produced by a number of cellular oxidative

metabolic processes including oxidative phosphorylation by the mitochondrial respiratory chain, xanthine oxidase, NAD(P)H oxidases, monoamine oxidases, and metabolism of ArAc by lipoxygenases (LOX) and cyclooxygenases (COX). Low levels of ROS are important in physiological processes, but increased production of ROS or loss of antioxidant defenses leads to progressive cell damage, decline in function and ultimately cell death. ROS can further stimulate release of cytokines that cause up-regulation of adhesion molecules, mobilization and activation of leukocytes, platelets and endothelium.

The activated inflammatory cells also release cytokines, MMPs, nitric oxide and additional ROS. Astrocytes, microglial cells and macrophages, synthesize and release ArAc metabolites, which increase vascular permeability, modulate inflammatory cell activities and ROS generation.

The vulnerability of the brain to oxidative stress is observed as it contains high concentrations of PUFA that are susceptible to lipid peroxidation and has lower antioxidant defenses compared to other organs. Oxidative stress appears as a component of many neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, Multiple Sclerosis, and Amyotrophic Lateral Sclerosis. [3]
Antioxidant therapies in MS are showing promising results, just like the therapeutic options used in MS is Dimethyl Fumarate or DMF, that in addition to having an immunomodulatory effect is also a potent antioxidant agent. It is thought to reduce oxidative stress through the NRF-2 (nuclear factor erythroid derived 2-related Factor 2) pathway and hence have a neuroprotective effect. Therefore it has recently been proposed that some of the therapeutic effects of DMF in MS are mediated by HCA_2, a G protein-coupled receptor, which is expressed in white and brown adipose tissue as well as in various immune cells. HCA_2 is activated by the keton body and endogenous neuroprotectant BHB with an EC50 of about 700 mM, mediating the neuroprotective, anti-inflammatory and immunomodulatory effects of a ketogenic diet. [2]

The Role of Mitochondria in MS

The generation of ROS may contribute also to mitochondrial dysfunction. Animal models suggest that mitochondrial injury may be a necessary step preceding axonal degeneration and it's thought to play a central role in the neurodegenerative disease process and in the pathogenesis of MS. [4] In MS hypoxia induced mitochondrial dysfunction in excitable demyelinated axons, which leads to decreased ATP production. This promotes axonal atrophy, leading to degeneration. Degenerating axons in progressive MS are seen to contain dysfunctional mitochondria and low levels of the transcriptional cofactor PGC-1a, which plays a key role in the activation of nuclear transcription factors involved in mitochondrial functions. [5] Furthermore, down-regulation of mitochondrial uncoupling protein (UCP) activity in EAE was shown to induce serious motor disability. The role of mitochondrial dysfunction in neurodegeneration suggests that targeting mitochondrial function may be a useful therapeutic strategy for progressive MS. Coenzyme Q10 has antioxidant properties and forms part of the electron transport chain interacting with complex I. A randomized placebo-controlled double-blind study of Coenzyme Q10 supplementation over 12 weeks in patients with relapsingand remitting MS demonstrated a reduction in IL-6 and MMP-9 levels. [6] The results of another similar trial by the same group demonstrated a reduction in depression and fatigue. [7]

Glucose Hypometabolism in MS

A decline in mitochondrial function may reflect in a glucose hypometabolism. Many researchers have suggested that there may be a bioenergetic shift taking place within neuronal metabolism where glucose uptake and utilization become progressively reduced. The shift has been observed to occur long before the onset of clinical signs of neurodegeneration, suggesting the possibility that glucose hypometabolism may be the initial step leading to axonal atrophy and neuronal loss through a reduction in ATP availability. The bioenergetic shift appears to specifically affect the metabolism of glucose. No such shift is seen with ketone body metabolism. This would suggest a potential therapeutic advantage in boosting energy supply

through an alternative route, such as ketone metabolism. A study that compared 47 MS patients with varying levels of fatigue and 16 healthy controls showed that the patients had reduced cerebral glucose metabolism in various regions within the brain, including the prefrontal, premotor, and supplementary motor areas and the putamen when compared to control subjects. There was an inverse correlation between degree of fatigue and glucose metabolic rate. [8]

Extramitochondrial metabolism increases in the presence of impaired mitochondrial metabolism of glucose. In a pilot study comparing 85 patients with relapsing and remitting MS and 54 patients with secondary progressive MS as well as 18 healthy controls, extramitochondrial glucose metabolism showed a correlation with disease progression, suggesting that impaired mitochondrial metabolism of glucose may play a significant role in disease progression in progressive MS. [9] Further molecular evidence of impaired glucose metabolism playing a role in MS is seen in the altered distribution of glucose (GLUT) and monocarboxylate transporters (MCT) within chronic lesions of MS where there is a decline in axonal GLUT3 and MCT2 expression. These changes may confer resistance to glucose entry into demyelinated axons, depriving them of adequate fuel supply resulting in glucose hypometabolism, [10] and showing a positive impact on MS disorders.

Diet and neurological disorders

KD may prevent and remediate cognitive deficits in neurological disorders because that consumption of a Western diet, high in saturated fat, refined sugar, and processed foods, impairs learning and memory and is associated with oxidative stress, inflammation, and mitochondrial dysfunction. Although neurological conditions, such as epilepsy, multiple sclerosis, and traumatic brain injury, have distinct disease processes, each exhibit increased oxidative stress, neuroinflammation, and disrupted energy metabolism. So that these pathophysiological factors can be influenced by dietary means, altering the course and outcomes of MS. Preservation of cognition is often a predominant concern for patients with neurological disorders. [11]

Ketogenic Diet

The possibility that providing the brain with an alternative source of fuel may reduce the rate of neurodegeneration is a promising avenue to explore. In 1967, Cahill et al. demonstrated that, during prolonged fasting, the body provides the brain with an alternative source of fuel, in the form of ketone bodies. The CNS is unable to use fat as a direct energy source and after prolonged carbohydrate restriction, fat is converted into ketone bodies in a process referred to as "ketogenesis." Ketogenesis takes place primarily within the matrix of mitochondria located within the liver and results in the production of the ketone bodies BHB, acetoacetate, and acetone which can easily cross the BBB and replace glucose as the brain's main sources of fuel. [12] Ketones bypass the glycolytic pathway and directly enter the Tricarboxylic Acid (TCA) cycle within mitochondria, contributing to anaplerosis. This shift in energy metabolism appears to reset cellular metabolic dysfunction and neuronal activity, although the exact mechanisms remain unclear. Many researchers propose that ketone body generation alters metabolism of neurotransmitters such as glutamate and gamma-amino butyric acid (GABA), improves mitochondrial function, decreases oxidative stress, and activates energy-sensing signaling pathways such as the peroxisome proliferator-activated receptor (PPAR), mammalian target of rapamycin (mTOR), and AMP-activated kinase (AMPK) pathways. [11]

The ketogenic diet, high in fat and low in carbohydrates, typically at a ratio of 3–4:1, has traditionally been used for the treatment of resistant epilepsy, but it is increasingly becoming apparent that its benefits may apply to all neurological disease in which the pathogenesis is influenced by abnormalities in cellular energy utilization.

There are 2 putative mechanisms that are proposed to underlie the beneficial effects of ketogenic diet on neurological function:

- First, ketogenic diet reduces oxidative stress by decreasing reactive oxygen species, increasing levels of antioxidant agents, increasing mitochondrial biogenesis, and reducing inflammation.

- Second, ketones offer an alternative to glucose as a source of fuel to the brain and the efficacy of a ketogenic diet in patients deficient for the glucose transporter GLUT1 at the BBB has been verified. Ketogenic diets could cause changes in the way the brain's energy levels are used, increasing the medium-chain triglycerides (MCT)1 and MCT4 transporters, which are responsible for transporting ketone bodies through the BBB, especially in the hippocampus and the prefrontal cortex, regions which are deteriorated in MS patients.

Neuroprotective properties of a ketogenic diet

The neuroprotective properties of the KD have been highlighted in a growing number of experimental models. The mechanisms remains unclear, one possibility is that the KD decreases ROS production by increasing the expression and activity of mitochondrial uncoupling proteins (UCPs), specifically the activity of UCP2, UCP4, and UCP5. Although the uncoupling may incur a small reduction in ATP generated through oxidative phosphorylation, its overall net effect is to enhance respiration and ATP levels through a reduction in ROS formation and protection from apoptotic events. [13] Moreover KD increases levels of antioxidant agents including catalase and glutathione through its inhibitory action on histone deacetylases (HDACs) and activation of the Nrf2 pathway. [14] J.B. Milder et al. show that when the ketogenic diet is first initiated, there is a temporary increase in oxidative stress. This may be activating Nrf2, since, a week after the temporary rise in oxidative stress, there is increased expression of Nrf2. Three weeks after the start of the diet, oxidative stress declines to below baseline levels and Nrf2 remains raised. [15]

A ketogenic diet also appears to preserve ATP levels in the event of mitochondrial respiratory chain dysfunction, caused by a defect in complex I of the electron transport chain, through the replenishment of TCA cycle intermediates. BHB is thought to increase levels of the TCA intermediate succinate, which bypasses complex I when entering the TCA cycle. This carries considerable implications for MS, since defects in the electron transport chain have been observed in white matter lesions as well as in "normal" regions of the motor cortex. [16]

Several other important mechanisms contribute to the neuroprotective consequences of calorie restriction, including decreased activity of proapoptotic factors, and inhibition of inflammatory mediators such as interleukins and tumor necrosis factor alpha (TNFα). Many of these mechanisms are thought to relate principally to the KD's anticonvulsant effects, but some if not all of them could contribute to cellular homeostasis and preventing neuronal injury or dysfunction. [17]

In a study, Kim DY et al. found that impairment of spatial learning and memory in vivo and synaptic plasticity in vitro correlated closely with increased cytokine/chemokine expression and ROS generation.

They observed that the KD significantly dampened motor disability, CNS inflammation and memory dysfunction in EAE mice. The neuroprotective effects of the KD may be mediated by a reduction in lymphocyte proliferation and cytokine/chemokine expression. The KD treatment increased the differentiation of Treg cells and led to a concomitant decrease in IL-6 and Th17 cell generation in EAE. Earlier studies have shown elevations in hippocampal glutathione peroxidase activity and catalase levels induced by the KD. MR imaging studies have helped solidify the concept that the memory impairment seen in MS patients is closely related to structural brain changes, notably the CA1 hippocampal region in humans becomes atrophic in the early stages of MS which then spreads to adjacent areas. Kim DY assert that the KD suppressed the expression of inflammatory cytokines and enhanced CA1 hippocampal synaptic plasticity and long-term potentiation, which resulted in improved learning, memory, and motor ability.

The anti-inflammatory effect of a KD may partly be explained through the inhibition of the NLRP3 inflammasome by BHB in a manner that is independent of starvation-induced mechanisms such as AMPK, autophagy, or glycolytic inhibition. The NLRP3 inflammasome is responsible for the cleavage of procaspase-1 into caspase-1 and the activation of the cytokines IL-1β and IL-18. Its inhibition prevents IL-1β andIL-18 generation and their downstream effects. [18]

In a different study In Young Choi et al. show that periodic 3day cycles of a fasting mimicking diet (FMD) are effective in ameliorating demyelination and symptoms in a EAE model.

The FMD improved the clinical picture in all mice. These improvements can be explained by increased corticosterone levels and Treg cell number, reduced levels of pro-inflammatory cytokines and antigen presenting cells (APCs). Furthermore, the FMD induced remyelination in axons in both EAE and MS models, showing its effects on both suppression of autoimmunity and remyelination.

Preliminary data suggest that a FMD or a chronic KD are safe and likely to be effective in the treatment of MS. [19]

Hormones in a Ketogenic Diet

There are other metabolic players that may be relevant to EAE. Many hormones are elaborated and altered by KD treatment. After chronic calorie restriction adiponectin increases and leptin decreases. Previous studies have demonstrated that upregulation of adiponectin suppressed inflammatory mediators and led to weight loss, whereas increased leptin expression correlated with a pro-inflammatory action. Thus, it appears that a metabolic treatment such as the KD or calorie restriction induces changes in specific hormones that positively modulate neuroinflammation. [20]

Many researchers relate ketone bodies to an increase in satiety. The mechanism on which this satiety effect is based is complex and depends on the relation that is established with several hormones and metabolites, mainly on a peripheral level. Yet, the effect of fat oxidation by astrocytes at the brain level seems particularly relevant because they produces ketone bodies that activate the ventromedial nucleus of the hypothalamus, which is directly related to satiety. Medium-chain triglycerides (MCTs) made up of medium-chain fatty acids (MCFAs) are the most important source for ketone bodies. MCFAs have a high oxidation rate to obtain energy, enhancing further energy use and weight loss without long-term recovery. The satiating effect, the feeling of hunger, may correct energy balance. This feeling depends on several metabolites and hormones, amongst which is ghrelin.

This hormone is a powerful appetite stimulator. It is produced in the stomach and can cross the BBB, joining its specific receptor (GHS1a) and activating the Y neuropeptide. Therefore, a rapid increase in ketone bodies leads to a significant decrease in ghrelin secretion and consequently reduce appetite. Unlike many weight loss diets can cause ROS generation related to cell damage, accelerated ageing and neurodegenerative diseases, ketogenic diets have shown improvements in metabolic and inflammatory markers and antioxidants. [21]

Human Studies

Many researchers' studies have been carried out to evaluate the benefits of ketones and ketogenic diet in neurodegenerative disorders.

Swidsinski A. et al. investigated the impact of dietary treatment on the Colonic Microbiome of MS patients demonstrating the involvement of the colonic microbiome in obesity, endocrine, inflammatory, and auto-immune disorders. The enormous variety of the healthy microbiome conveys antigenic diversity to the host shaping its immunity and autoimmunity. They compared the composition of the colonic microbiota quantitatively in 25 MS patients and 14 healthy controls using fluorescence in situ hybridization (FISH) with 162 ribosomal RNA derived bacterial FISH probes. Ten of the MS patients received a ketogenic diet for 6 months.

Changes in concentrations of 35 numerically substantial bacterial groups were monitored at baseline and at 2, 12, and 23/24 weeks. The total concentrations and diversity of substantial bacterial

groups were reduced in MS patients, so they state that colonic microbiome and neuropathology are closely interrelated and the KD for 6 months completely restored the microbial biofermentation mass and is an interesting interventional tool for prospective clinical studies. [22]

In a later study M. Bock et al. explored the impact of an Adapted ketogenic diet (AKD) and Calorie restriction (CR) on gene expression of biosynthetic enzymes for pro- (ALOX5, COX1, COX2) and anti-inflammatory (ALOX15) eicosanoids in patients with relapsing-remitting MS. Pro-inflammatory eicosanoids have been implicated in the pathogenesis of MS since they increase vascular permeability and induce leukocyte migration into the brain. In the clinical trial 24 patients were randomly allocated into 3 groups: 8 controls, 5 on CR and 11 on AKD for 6 months. Inter-group comparison indicated that expression of the pro-inflammatory ALOX5 in the pooled treatment group was significantly reduced when compared with the control group.

Intra-group comparison showed reduced expression of pro-inflammatory enzymes, such as COX1 and COX2, and a positive correlation between expression of pro-inflammatory ALOX5 and COX2 and an inverse correlation of ALOX5 and COX1 expression. In conclusion, a KD diet can reduce the expression of enzymes involved in the biosynthesis of pro-inflammatory eicosanoids. [23]

A recent study published in May 2019 M. Benlloch et al. evaluate the satiating Effect of a Ketogenic Diet and Its Impact on Muscle Improvement and Oxidation State in MS Patients. A pilot study was carried out with 27 MS patients who were given a Mediterranean isocaloric and ketogenic diet for 4 months. Anthropometric measurements were carried out, the satiety and hunger perception was assessed, the levels of oxidation markers, such as BHB and paraoxonase 1 (PON1), were measured by spectrophotometric automated assays; finally ghrelin was determined by an enzyme immunoassay in the serum. All measurements were taken before and after surgery. The results show that ketone bodies can improve motor function, as a result of their neuroprotective properties. Another reason is related to the metabolic impact based mainly on the satiating effect and the weight loss with an increase in lean mass and a decrease in fat mass. Moreover, there was a significant increase in PON1 levels, associated with low levels of oxidative stress and inflammation. It becomes clear that the satiating effect has a positive impact on the clinical evolution of MS. [21]

Conclusions

In conclusion, we can assert that KD significantly attenuates brain inflammation and reverses both memory dysfunction and motor impairment. There are many evidences that metabolic substrates (and certain hormones) can reduce inflammatory responses, and as a consequence provide both structural and functional neuroprotective effects. This type of diet may represent a therapeutic alternative by supplementing the pharmacological treatment. Patients with MS may readily benefit from this non-pharmacological treatment option.

However, new studies would be required to confirm the conclusions drawn and the mechanisms proposed. Current ketogenic diet protocols involve a range of options, which encourages patient compliance and offer a palatable therapeutic option. Supplementation with ketones to induce ketosis has also shown an acceptable safety and tolerability profile. Current treatment options in MS affect immune function and relapse rate with little effect on disease progression. They are sometimes accompanied with significant side effects including lymphopenia, multifocal leukoencephalopathy, and malignancy. Consequently, it may be more favourable for some patients to pursue a relatively risk-free dietary approach that has the potential to reduce disease progression without affecting immune response. Mitochondria-targeting agents, ketones, and the ketogenic diet have shown positive results in several models of neurodegeneration, and the relatively safe option of a ketogenic diet deserves further investigation.

Of course, it will, also hopefully allow more consideration be put into the coding of neuroinflammation deseases for research studies to allow the recordered information to be more accurate more retrievable and more useable in the future.

References

1. Storoni, M., & Plant, G. T. (2015). The therapeutic potential of the ketogenic diet in treating progressive multiple sclerosis. Multiple sclerosis international, 2015.
2. Offermanns, S., & Schwaninger, M. (2015). Nutritional or pharmacological activation of HCA2 ameliorates neuroinflammation. Trends in molecular medicine, 21(4), 245-255.
3. Adibhatla, R. M., & Hatcher, J. F. (2008). Altered lipid metabolism in brain injury and disorders. In Lipids in health and disease (pp. 241-268). Springer, Dordrecht.
4. Nikić, I., Merkler, D., Sorbara, C., Brinkoetter, M., Kreutzfeldt, M., Bareyre, F. M., ... & Kerschensteiner, M. (2011). A reversible form of axon damage in experimental autoimmune encephalomyelitis and multiple sclerosis. Nature medicine, 17(4), 495-499.
5. Witte, M. E., Nijland, P. G., Drexhage, J. A., Gerritsen, W., Geerts, D., van het Hof, B., ... & van Horssen, J. (2013). Reduced expression of PGC-1α partly underlies mitochondrial changes and correlates with neuronal loss in multiple sclerosis cortex. Acta neuropathologica, 125(2), 231-243.
6. Sanoobar, M., Eghtesadi, S., Azimi, A., Khalili, M., Khodadadi, B., Jazayeri, S., ... & Aryaeian, N. (2015). Coenzyme Q10 supplementation ameliorates inflammatory markers in patients with multiple sclerosis: a double blind, placebo, controlled randomized clinical trial. Nutritional neuroscience, 18(4), 169-176.
7. Sanoobar, M., Dehghan, P., Khalili, M., Azimi, A., & Seifar, F. (2016). Coenzyme Q10 as a treatment for fatigue and depression in multiple sclerosis patients: a double blind randomized clinical trial. Nutritional neuroscience, 19(3), 138-143.
8. Roelcke, U., Kappos, L., Lechner-Scott, J., Brunnschweiler, H., Huber, S., Ammann, W., ... & Radii, E. W. (1997). Reduced glucose metabolism in the frontal cortex and basal ganglia of multiple sclerosis patients with fatigue: A 18F-fluorodeoxyglucose positron emission tomography study. Neurology, 48(6), 1566-1571.
9. Regenold, W. T., Phatak, P., Makley, M. J., Stone, R. D., & Kling, M. A. (2008). Cerebrospinal fluid evidence of increased extra-mitochondrial glucose metabolism implicates mitochondrial dysfunction in multiple sclerosis disease progression. Journal of the neurological sciences, 275(1-2), 106-112.
10. Nijland, P. G., Michailidou, I., Witte, M. E., Mizee, M. R., van der Pol, S. M., van Het Hof, B., ... & van Horssen, J. (2014). Cellular distribution of glucose and monocarboxylate transporters in human brain white matter and multiple sclerosis lesions. Glia, 62(7), 1125-1141.
11. Francis, H. M., & Stevenson, R. J. (2018). Potential for diet to prevent and remediate cognitive deficits in neurological disorders. Nutrition reviews, 76(3), 204-217.
12. Owen, O. E., Morgan, A. P., Kemp, H. G., Sullivan, J. M., Herrera, M. G., & Cahill, G. J. (1967). Brain metabolism during fasting. The Journal of clinical investigation, 46(10), 1589-1595.
13. Sullivan, P. G., Springer, J. E., Hall, E. D., & Scheff, S. W. (2004). Mitochondrial uncoupling as a therapeutic target following neuronal injury. Journal of bioenergetics and biomembranes, 36(4), 353-356.
14. Shimazu, T., Hirschey, M. D., Newman, J., He, W., Shirakawa, K., Le Moan, N., ... & Newgard, C. B. (2013). Suppression of oxidative stress by β-hydroxybutyrate, an endogenous histone deacetylase inhibitor. Science, 339(6116), 211-214.
15. Milder, J. B., Liang, L. P., & Patel, M. (2010). Acute oxidative stress and systemic Nrf2 activation by the ketogenic diet. Neurobiology of disease, 40(1), 238-244.
16. Lu, F., Selak, M., O'Connor, J., Croul, S., Lorenzana, C., Butunoi, C., & Kalman, B. (2000). Oxidative damage to mitochondrial DNA and activity of mitochondrial enzymes in chronic active lesions of multiple sclerosis. Journal of the neurological sciences, 177(2), 95-103.

17. Rho, J. M., & Stafstrom, C. E. (2012). The ketogenic diet as a treatment paradigm for diverse neurological disorders. Frontiers in pharmacology, 3, 59.
18. Hao, J., Liu, R., Turner, G., Shi, F. D., & Rho, J. M. (2012). Inflammation-mediated memory dysfunction and effects of a ketogenic diet in a murine model of multiple sclerosis. PloS one, 7(5), e35476.
19. Choi, I. Y., Piccio, L., Childress, P., Bollman, B., Ghosh, A., Brandhorst, S., ... & Wei, M. (2016). A diet mimicking fasting promotes regeneration and reduces autoimmunity and multiple sclerosis symptoms. Cell reports, 15(10), 2136-2146.
20. Matarese, G., Moschos, S., & Mantzoros, C. S. (2005). Leptin in immunology. The Journal of Immunology, 174(6), 3137-3142.
21. Benlloch, M., López-Rodríguez, M. M., Cuerda-Ballester, M., Drehmer, E., Carrera, S., Ceron, J. J., ... & de la Rubia Ortí, J. E. (2019). Satiating effect of a ketogenic diet and its impact on muscle improvement and oxidation state in multiple sclerosis patients. Nutrients, 11(5), 1156.
22. Swidsinski, A., Dörffel, Y., Loening-Baucke, V., Gille, C., Göktas, Ö., Reißhauer, A., ... & Bock, M. (2017). Reduced mass and diversity of the colonic microbiome in patients with multiple sclerosis and their improvement with ketogenic diet. Frontiers in microbiology, 8, 1141.
23. Bock, M., Karber, M., & Kuhn, H. (2018). Ketogenic diets attenuate cyclooxygenase and lipoxygenase gene expression in multiple sclerosis. EBioMedicine, 36, 293-303.