



# **The Potential Therapeutic Role of the Ketogenic Diet in Multiple Sclerosis**

Brandon Fell

The Ohio State University

College of Education and Human Ecology

Master of Science Exercise Physiology

April 2020

## **OSU Advisor and Committee Members**

Dr. Jeff Volek

Dr. William Kraemer

## Table of Contents

<b>ABBREVIATIONS.....</b>	<b>3</b>
<b>BACKGROUND OF MS.....</b>	<b>3</b>
History of MS.....	3
Defining MS and its subtypes.....	3
Prevalence and Demographics.....	4
Treatment Options.....	4
Pathophysiology.....	4
Metabolism.....	5
<b>BACKGROUND OF THE KETOGENIC DIET.....</b>	<b>6</b>
Defining the KD.....	6
Methods of Ketosis.....	7
Benefits of Ketones.....	7
<b>HOW CAN THE KETOGENIC DIET IMPROVE OUTCOMES OF MS.....</b>	<b>9</b>
Energy Demands & Inflammation.....	9
Ketones and Energy Rescue.....	10
Future Implications.....	10
<b>REFERENCES CITED.....</b>	<b>11</b>

## ABBREVIATIONS

βHB	Beta Hydroxybutyrate
AcAc	Acetoacetate
MS	Multiple Sclerosis
KME	Ketone Monoester
KDE	Ketone Diester
CNS	Central Nervous System
GLUT	Glucose Transporter
ATP	Adenosine Triphosphate
RRMS	Relapsing and Remitting Multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis
PRMS	Progressive Relapsing Multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
TCA	Tricarboxylic Acid Cycle
ETC	Electron Transport Chain
MCT	Monocarboxylic Transporter
PDH	Pyruvate Dehydrogenase
ROS	Reactive Oxygen Species
NF-κB	Nuclear Factor kappa B
T25-FW	Timed 25 Foot Walk
ECF	Extra Cellular Fluid
KE	Ketone Ester
KS	Ketone Salt
USG	Urine Specific Gravity
MSFC	Multiple Sclerosis Functional Composite
USDA	United States Department of Agriculture

## BACKGROUND OF MULTIPLE SCLEROSIS

Historical descriptions of Multiple Sclerosis (MS) date back as far as the Middle Ages, but the disease as we know it became designated in 1868 by Jean-Martin Charcot, a professor of Neurology at the University of Paris who referred to the condition as *sclérose en plaques* (Kumar, 2011). There are four types of MS which include Primary Progressive MS (PPMS), Secondary Progressive MS (SPMS), Progressive-Relapsing MS (PRMS), and Relapsing-Remitting MS (RRMS). RRMS, the most common, is an incurable autoimmune disease of the central nervous system (CNS) characterized by unpredictable attacks which may yield permanent neural impairments yet may also be followed by years of remission. MS is characterized by inflammation, demyelination, and progressive neurodegeneration. MS damages the myelin sheath covering of CNS nerves, disrupting communication between the brain and body and creating lesions due to repeated inflammation.

The United States had the highest prevalence of MS at 400,000 – and this was before the results of a recent study reported more than double the previously indicated prevalence (Culpepper et al., 2019). Of all neurological conditions considered in a nationwide health report, MS represented the worst life expectancy at 25-35 years after initial diagnosis, which occurs on average at age

34. 66 years is the current mean life expectancy with the disease, which is seven years shorter of a life expectancy than those without the disease (Mawer, 2018; Madell, 2018).

MS is not contagious nor inherited, but there are a few factors based on epidemiological studies which may help elucidate the causes such as gender, genetics, age, geography and ethnicity (Wallin et al., 2019). Recent studies have shown MS to be three times more likely in women than men, perhaps eliciting a hormonal cue toward disease acquisition. Regarding genetics, the International MS Genetics Consortium found MS risk to be correlated in up to 200 allelic variants with a general population risk of .1%, a child with one MS-positive parent to be 2%, and a child with two MS-positive parents to be 12.2% (ASHG, 2016 & Compston, 2008). Although diagnosis is typically between age 20 and 50, MS can also occur in children and older adults. Prevalence seems to be higher as distance from the equator increases, yet this theory becomes slightly distorted when controlling for ethnicities. MS occurs in most ethnic groups yet is most common in Caucasians of northern European descent and African American females (Wallin et al., 2019).

It has only been twenty-five years since the introduction of the first treatment option – interferon beta-1b – which aims to reduce the number of inflammatory cells crossing the blood brain barrier (BBB). Better treatment options are now available and include FDA approved disease modifying therapies which have reduced relapses and delayed disability progression as evidenced by clinical trials. Medications to specifically target flare-ups may be administered in injectable, oral, or infused form, and management of subsequent MS side effects are aimed at bladder problems, bowel dysfunction, depression and mood changes, fatigue, itching, general pain, sexual problems, spasticity and tremors (Doshi, 2017 & Sorenson, 2017).

Current treatment options target management of the sporadic inflammatory flare-ups and largely include oral or intravenous corticosteroids, plasma exchange, and chemotherapy. Management of symptoms is the crux to preserve an imminently declining quality of life. The administered medications target myriad of physiological outcomes aimed at reducing flareups, time to exacerbation, and modulation of the immune response. These include FDA approved interferon beta-1a/b, T-cell, B-cell and macrophage suppression, pyrimidine synthesis inhibition, lymphocyte retention, and antioxidant neuroprotection (National MS Society, 2020).

As with many conditions, a proposed modality to improve quality of life lies inherently in physical activity. This “treatment” poses a challenge to a population characterized by fatigue, psychomotor impairments, inflammation, and compromised immune systems. Although MS patients are trapped in a vicious cycle of fatigue and subsequent lack of desire or ability to exercise, growing evidence continues to reveal significant improvements in fatigue scores for those who engage in *some* type of exercise. Prescribing the modality and intensity of exercise poses a challenge due to the wide continuum of disease progression existing in this population. A recent meta-analysis of 31 articles assessed outcomes of fatigue after physical exercise in MS patients. Importantly, the outcomes included a host of modalities ranging from aquatics, to aerobics, to resistance training, all of which showed a significant improvement in fatigue scores post-intervention (Razazian et al., 2020). These findings provide support that we can use a clinical trial to improve MS treatment outcomes using physical activity plus other adjuvant interventions to augment positive results.

The production of lactate (i.e. exercise) has been a proposed substrate capable of rectifying a multitude of maladies seen in neurologic disorders. While lactate is often demonized in remedial conversations of exercise physiology and metabolism, it is characterized by a few important functions. Some of these roles may be beneficial to a population such as MS where prominent

features include metabolic deficits as evidenced by impaired glucose tolerance (IGT) (Wens et al., 2017).

Lactate is the final product of anaerobic glycolysis where an accumulation of cytosolic pyruvate exceeding the capacity of the TCA cycle may be rescued by lactate dehydrogenase (LDH). Oxidative phosphorylation functions to generate ATP dependent on oxygen and NADH availability. Lack of oxygen inhibits oxidative phosphorylation ATP turnover and promotes NADH accumulation in the TCA cycle. This allows NADH to inhibit the committed step of the TCA cycle, the pyruvate dehydrogenase enzyme (PDH).

As mentioned, LDH is an alternative pathway within glycolysis resulting in a net loss of 4 ATP and a gain of NAD<sup>+</sup>. The energy cost of making lactate can lower the ATP/ADP ratio and increase the NAD/NADH ratio, allowing TCA and oxidative phosphorylation to continue once most lactate is metabolized. The tandem product of NAD<sup>+</sup> with the enzymatic consumption of H<sup>+</sup> acts as a buffer allowing lactate to then be picked up quickly in the blood, thereby generating a flux for glycolysis to continue.

In healthy individuals blood lactate is stable, which is a product of the balance between the lactate released into blood and that which is cleared by the blood from the liver and kidneys. Exercise induced hyperlactatemia (> 8 mmol/L) is a distinct metabolic state from lactatemia observed at rest (0.5-1.0 mmol/L) (Goodwin et al., 2007). When exercise is introduced, lactate production by muscle cells exceeds that of available oxygen (where exercisers typically attribute their writhing pain during intense exercise).

When focusing upon the noted impairments seen in MS metabolism, the focal issue seems to be on IGT and subsequent failure of glucose transporters to meet the needs of ailing CNS neurons (Wens et al., 2017). While the potential to circumvent a glycolytic energy deficit supplied by predominantly fat yields a provocative dietary approach, the potentials of lactate as an energy substrate is also warranted.

The GLUT impairment seen in CNS disorders illuminates an alternative requisite pathway for brain energy. Preliminary evidence shows under both resting and hyperlactatemic conditions (i.e. exercise) the brain is capable of both uptake and oxidation of lactate for fuel (van hall et al., 2009). Although this has been noted in retinal cells, it warrants investigation based on the anatomic location of these cells and functionality in neural signaling. This is further elucidated by the fact that lactate has been shown to spare glucose as a fuel for neurons (Dienel, 2011).

As lesions mount amid MS progression, neural signaling becomes interrupted affecting both cognition and motor functionality. Growing evidence suggests (in part) this can be attributed to problems associated with glutamate – the most abundant excitatory neurotransmitter of our CNS, helping to form memories in the brain yet is also toxic to neurons (Lewerenz, 2015). Fasting hypoglycemia, common in MS may further exacerbate glutamate concentrations surrounding neurons as blood glucose is a primary means of glutamate removal (Luo, et al., 2001). Lactate has been shown to protect against glutamate excitotoxicity and ischemia, two outcomes not often spoken in the same breath as MS, yet pathophysiologic connections can be made (Helmenstine 2019 & Vohra, 2019). Moreover, noting the cognitive decline which accompanies motor impairment, lactate expresses an integral role in long-term memory formation (Mason, 2017).

The BBB is (appropriately) a highly selective permeable membrane overseeing equality between entrance and exit of this highly regarded boundary, strictly regulating brain homeostasis. Any type of disruption between the strict supervision of endothelial cells and subsidiary astrocytes,

pericytes, neurons, and glial cells which coincide with tight junctions may equate to major imbalances. In neurologic disorders, the BBB is disrupted which exposes this tollgate. The administration of medications amplifies the duality of the BBB, hedging the acute efficacy and desired outcomes against future immune attacks.

The endothelial cells of the BBB line the interior of blood vessels, which are then subdivided into the luminal and abluminal sides. The transporters which lie on these membranes are highly specific for the transport of nutrients into, and waste removal from the CNS (Mittapalli et al., 2010). These cells contain substantial mitochondria, correlating to ATP generation potential and rescue of energy deficiencies noted in MS patients. Importantly, the endothelial cells of the CNS express low concentrations of leukocyte adhesion molecules, thereby limiting the number of immune cells which can enter the CNS (Daneman et al., 2010). This strict regulation again has pros and cons by allowing and disallowing what may be necessary to rescue metabolic deficiencies.

To summarize, current treatment options include oral or intravenous corticosteroids, plasma exchange, chemotherapy – and most recently a push for physical activity. Each of these (in some capacity) target a reduction in inflammation and improvement in quality of life. However, few studies exist assessing the efficacy of macronutrient manipulation to monitor these side effects of disease progression. Current dietary recommendations for MS focuses on the United States Department of Agriculture's (USDA) MyPlate guidelines, which suggests a plate balanced with fruits and vegetables, whole grains, and lean protein all low in fat or fat-free along with minimal saturated fat (National MS Society, 2019 & USDA, 2020). This diet plan is abundant in carbohydrate, moderate in protein, and low in fat.

These steadfast governmental mandates (declared uniform for healthy and diseased populations alike) present an opportunity for patients with MS to manipulate their macronutrient distribution by lowering carbohydrate and increasing dietary fat, citing the inability of this population to efficiently transport and use glucose as a fuel in the CNS. This metabolic deficiency attributes to the fatigue, inflammation, and adverse psychomotor symptoms seen in MS. Moreover, the ketogenic diet (KD) can become a powerful treatment tool in providing ownership to a patient's personal disease management (*AJMC*, 2018).

## **BACKGROUND OF THE KETOGENIC DIET**

The KD, almost of a polar image of the USDA guidelines, is characterized by high fat, moderate protein, and very low carbohydrate intake. During periods of prolonged fasting, calorie restriction, intense exercise, or adherence to the KD, the ketone bodies beta hydroxybutyrate ( $\beta$ HB) and Acetoacetate (AcAc) are endogenously produced from the liver to meet the energy demands of the brain, heart, skeletal muscle and peripheral tissues (Cahill, 2003). The consumption of a mixed diet containing significant carbohydrate yields suppressed ketone levels, typically below ( $< 0.1\text{mM}$ ), which prohibits ketones to then function as a metabolic fuel to facilitate Adenosine Triphosphate (ATP) generation (Sato, Kashiwaya et al. 1995).

The potency of ketones have tenured roots in the safe and effective treatment of the neurodegenerative disorder epilepsy, but is now emerging as a nutrition intervention for a multitude of disease states including Metabolic Syndrome, Type 2 Diabetes Mellitus, Polycystic Ovary Syndrome, Alzheimer's, various cancers, and Pelizaeus-Merzbacher Disease (Masino, 2017 & Stumpf et al., 2019). These disease states all share a common thread of chronic inflammation, with the latter yielding a pathogenesis familiar to MS – damage to the CNS and an

energy substrate deficiency due to an inability of the cells' ability to use glucose as fuel. This suggests the KD may offer an alternative fuel source which is anti-inflammatory and assists with both energy production and apoptosis (Storoni & Plant, 2015).

On a KD, when carbohydrate and protein intake contribute less than ~20% of total energy intake, insulin levels are depressed, glucose concentration drops, and the ketogenic pathway accelerates resulting in a natural state of '*nutritional ketosis*', which is characterized by ketone concentrations between 0.5 and 2 mmol/L. Levels fluctuate throughout the day depending on exercise and food intake, and may transiently go as high as 5 mmol/L. Nutritional ketosis is therefore a product of accelerated fat oxidation, which coincides with desirable body composition improvements (Volek et al., 2004).

MS is characterized by impaired cognition and motor function, representing months to years of disease progression. To enjoy the potential benefits associated with adherence to a well-formulated KD, 2-4 weeks appear to be optimal for keto-induction, with >4 weeks for metabolic changes that reshape the hormonal milieu associated with a higher capacity for oxidizing fat and producing  $\beta$ HB. Because this may not always be feasible, it is worth exploring the ability to rapidly elevate blood ketones by ingesting  $\beta$ HB in supplement form. The resultant '*acute nutritional ketosis*' does not require a ketogenic diet or any carb and protein restriction. Supplemental ketones are absorbed from the gut into the circulation and thus does not involve increased hepatic ketogenesis. The level of ketosis varies depending on the form and the dose, but concentrations can acutely elevate into the range of nutritional ketosis. The effect is short-lived lasting a few hours, thereby requiring repeated dosing to sustain ketosis.

Exogenous ketones are preformed versions of  $\beta$ HB or precursors that break down into ketone bodies, raising blood  $\beta$ HB without the need for endogenous ketone production. Although the  $\beta$ HB delivered is from an external source, it is oxidized by the same pathway as endogenously produced  $\beta$ HB (Harvey et al., 2018 & Shaw et al., 2019). Exogenous ketones bypass the nutritional requirements of carbohydrate reduction to increase serum  $\beta$ HB. However, nutritional ketosis is a distinct metabolic state that requires underlying gene regulation to promote  $\beta$ HB production indefinitely and dependent on the entire food matrix.

Published data is suggestive that exogenous ketone supplements might have positive impacts on health and performance. For example, human studies of exogenous ketones have found beneficial effects on endurance exercise performance (Cox, Kirk et al. 2016), cognitive performance (Evans and Egan 2018), blood glucose control (Myette-Cote, Neudorf et al. 2018), response to immune challenges (Neudorf, Durrer et al. 2019) and cardiac function (Nielsen, Møller et al. 2019). Animal studies are more advanced, with data demonstrating efficacy in a range of conditions such as neurodegeneration (Kashiwaya, Bergman et al. 2013), mood disorders (Ari, Kovács et al. 2016), body weight control (Deemer, Davis et al. 2019), and inflammation (Youm, Nguyen et al. 2015).

Exogenous ketone supplementation exists in the form of ketone salts (KS) or ketone esters (KE). When packaged chemically as KE (Pinckaers et al., 2017), they can be consumed in higher doses because they are not limited by mineral loads. KE's increase blood ketones ~4-6mM  $\beta$ HB and may improve cognitive function due to concentration-dependent brain ketone uptake as well as impact inflammation and recovery processes related to exercise stress (Cunnane et al., 2011 & Stubbs et al., 2017). More than 10 years of research primarily done at the University of Oxford and NIH led to the development of a KE technology, which is now commercially available through a US-based company called HVMN.

Regardless of form, a brief discussion of the potency of physiologic ketone body signaling is warranted. The benefits are many, however this discussion will be confined to those characteristics which exude the most potential to rescue the deficits seen in MS. These include the anapleurotic potential, anti-inflammatory effects, antioxidant upregulation, and neuroprotective features. Keeping in mind the characteristic inflammation of MS patients, it is worth pointing out these themes of MS symptom-rescue seem to largely link to the suppression of reactive oxygen species (ROS) in some capacity.

#### *Anaplerosis:*

An alternative energy source to glucose is necessary for patients with MS. Ketones readily cross the BBB and spinal cord via monocarboxylase transporters (MCT's) to enter neuronal and glial cells. (Pierre and Pellerin, 2005). Upon ketone body entrance into these cells, there is an enzymatic production of two Acetyl-CoA molecules which become available for the TCA cycle. This pyruvate dehydrogenase (PDH) bypass step reduces glycolytic flux, electron transport chain (ETC) Complex-I activity, and inherent ROS production. It is also well-established ketone bodies induce mitochondrial biogenesis by upregulation of PGC1 $\alpha$  and SIRT3, augmenting ATP delivery to the CNS (Hasan-Olive et al., 2019).

#### *Anti-inflammatory*

There is little in the realm of KD interventions and MS, leaving current speculations to be based on animal models or similar neurodegenerative pathologies. However,  $\beta$ HB (specifically) appears to have direct effects in the regulation of inflammation. By inhibiting the cleavage of caspase 1 from the NLRP3 complex, a blunting of IL-1 $\beta$  and IL-18 is noted while also upregulating anti-inflammatory benefits (Youm et al., 2015). When macrophages were exposed with known agonists to toll-like receptors similar results were seen, potentiating the inhibition of the NF- $\kappa$ B inflammatory pathway. Importantly, these  $\beta$ HB-signaling findings were then applied to address functional recovery after spinal cord damage, and the authors found reduction in lesion volume along with improvements in grip strength, sticker removal, and gait analysis (de Rivero Vaccari et al., 2008). Referencing the Experimental Autoimmune Encephalomyelitis (EAE) MS model, mice were injected resulting in CNS neurodegeneration and synaptic deficiencies in the hippocampus. The experimental mice were fed the KD and showed improvement in motor function, previous cognitive impairments and memory, reduction in white matter lesions via MRI, substantially lowered levels of several cytokines (IL-6, TNF- $\alpha$ , IL-12, IL-17) and chemokines (Kim do et al., 2012). These results were noted both in blood and in the brain.

#### *Antioxidant*

Inflammation and oxidative stress are positively correlated. There exists a homeostatic imbalance between the production of ROS and the immune system's ability to efficiently and effectively protect the body through mechanisms such as superoxide dismutase (SOD) and catalase, which leads to chronic inflammation and a destruction of cells and tissues. In this state, antioxidant defenses are overwhelmed leading to ROS accumulation and potentially permanent damage done to proteins, membrane lipids, and nucleic acids. Growing evidence has demonstrated improvements in antioxidant activity resultant from the KD which combat the neuroinflammation and deficits seen in the mitochondria (Milder and Patel, 2012). Specifically, the KD has decreased levels of oxidation-reduction signaling molecules such as H<sub>2</sub>O<sub>2</sub> to activate Nrf2 protective factors (Wilson et al., 2005). Lastly,  $\beta$ HB has been recognized as a potent inhibitor of histone deacetylases (HDAC's) in mice, which increases the expression of SOD (Shimazu et al., 2013).

#### *Neuroprotection:*



Impaired learning and memory function are prominent clinical symptoms in patients with MS. Although research addressing the role of ketone bodies and MS has yet to be explicitly elucidated, the neuroprotective roles of murine models is promising. Again referencing the EAE mouse model, they were fed the KD to address this memory impairment which improved motor disability, CA1 hippocampal plasticity, and spatial learning. Excitingly, these KD-EAE mice showed reversal of both the hippocampus atrophy and lesions around the ventricles (Kim et al., 2012). These findings may be attributed to a mitigation of the noted immune response.

## HOW CAN THE KETOGENIC DIET RESCUE MULTIPLE SCLEROSIS?

Since the 1800's, it has been recognized that axonal damage defines the progression of MS, however it remains unclear whether this parallel's or precedes the diseases hallmark of axon sheath demyelination (De Vos et al., 2008). Current literature views these hallmark moieties of MS as either the "outside-in" approach or the "inside-out" approach, asking whether inflammation yields neurodegeneration or vice versa, respectively. During inflammatory-dependent demyelination, energy demands increase amid compromised mitochondrial activity. This effect has been described as "catch-up" as Na<sup>+</sup> ions can accumulate in the extra cellular fluid (ECF), subsequently impairing Na<sup>+</sup>/K<sup>+</sup>-ATPase pump activity in vitro. This imbalance eventually leads to the death of spinal cord neurons (Kurnellas et al., 2004). Because nerve cells are highly dependent on electrolyte balance for excitability and proper function, this abnormal outcome results in nerve cell apoptosis due to a deficit in oxidative phosphorylation-derived ATP available for active transport of Na<sup>+</sup> and K<sup>+</sup>.

Quality of life progressively declines as axonal lesions accumulate in the CNS, represented by psychomotor deterioration through the life span. This has been quantified at large through use of the Multiple Sclerosis Functional Composite (MSFC) in both clinical trials and physician care settings for over twenty years, with recent analysis citing its reliability, validity, and sensitivity. The pillars of the MSFC include quantification of cognitive function, ambulation, and arm/hand function which measures degree of disability. Therefore, diagnosis and proper measurement of pathogenesis light the path for early and ongoing multidisciplinary treatment plans. As medical visits and medications may provide financial burden, dietary intervention presents a multifaceted opportunity to both empower MS patients with an active tool in their own disease management, while augmenting their current treatment plan simply by nutrition modification.

The KD has demonstrated the ability to inhibit the NF-κB inflammatory pathway, decrease oxidative stress, and improve mitochondrial function and biogenesis, emerging as a plausible dietary approach in treating neurodegeneration associated with RRMS (Pinto et al., 2018). One study using MS mouse models demonstrated the KD suppressed inflammatory markers, resulting in improvements in both cognition and physical function (Kim et al., 2012). Additionally, growing evidence suggests that βHB can act as a signaling metabolite, directly and indirectly modulating receptor activation and gene expression in ways that have positive implications for lifespan and health span (Newman, Covarrubias et al. 2017, Newman and Verdin 2017).

During periods of prolonged fasting or dramatic carbohydrate restriction, human metabolism shifts to provide the brain with ketone bodies as a fuel source. Because the CNS is unable to use fat directly for fuel, this metabolic shift elicits *ketogenesis* which is the precursor to the production of ketone bodies. In fact, in vitro studies show a preference of βHB to glucose in the CNS (LaManna et al., 2010). Additionally, evidence suggests there is both impaired glucose tolerance and dysfunction of glucose transporters such as GLUT4 in the MS population (Wens et al., 2017).

Neurons of the adult brain demand the greatest amount of glucose-derived energy at ~20%, which further compounds MS pathogenesis in the wake of the energy deficit created by neurodegeneration and demyelination (Howarth et al., 2012). It is estimated oligodendrocytes of demyelinated axons require a five-fold energy demand compared to otherwise functioning axons (Neishabouri & Faisal, 2011), further highlighting the necessity to explore alternative sources of energy. A compromised ability exists to specifically use glucose as a fuel source for the immune system and healthy body functions.

Noting the MS prevalence demographics, recent advancements in the field of immunology have displayed important properties of immune cells, highlighting their ability to respond and bind to dietary metabolites including vitamin D and fatty acids, both of which are inherent components of a KD (Bhargava, n.d. & Li et al., 2009). Moreover, the KD is high in Monounsaturated Fatty Acids (MUFA) and saturated fatty acid yet low in pro-inflammatory  $\omega$ -6 Polyunsaturated Fatty Acid (PUFA), which satisfies a dietary requisite to not only exude anti-inflammatory properties but more importantly modulate proinflammatory metabolic pathways.

A brain energy deficit is represented by lesions, demyelination, and oligodendrocyte activity in conjunction with impaired glucose utilization, yet rescued by the priority of the brain to uptake ketones when available. When ketones are available to the brain, cognitive outcomes are improved both in cognitively impaired and hypoglycemic populations, thereby confirming the brain's preference to ketones over glucose and the overall safety of ketosis (Cunnane et al., 2016).

Observations from in vitro and in vivo studies suggest the KD may mitigate the neurodegeneration which precedes RRMS. The KD's purported ability to improve mitochondrial function could correct ATP availability and not only prevent the degeneration of axons but repair those which were damaged. The application of the KD appears to be so novel to the MS population that a review of dietary approaches to augment quality of life made no mention of the KD. Considering the devastating effects of this neurodegenerative disease, advancing the understanding of its pathogenesis is paramount.

Proper instruction of the KD requires education time and poses a potential limitation of adherence. Therefore, acute nutritional ketosis via exogenous ketone supplementation, which bares similar physiological effects of a ketogenic diet improves the documented psychomotor dysfunctions seen in patients with MS.

Multiple Sclerosis is an incurable inflammatory disease of the central nervous system which progressively deteriorates cognition, motor function, and overall quality of life. The growing pandemic prevalence of MS is met with both sound and inconsistent treatment options. Novel (or emerging) therapies will provide a solution to fix the primary limitations in MS treatments via pharmaceutical or lifestyle change innovations. Mouse models and CNS fMRI imaging have documented the maladies of MS, often citing impairments of neuronal glucose uptake and utilization. Ketones are a potential novel therapy which can rescue the glucose energetic gap in MS because  $\beta$ HB transport remains intact and can be used by the nervous tissues to fuel their NADH-dependent reactions. Current MS recommendations are not conducive to endogenous ketone production because carbohydrate guidelines are set too high; however, the opportunity to potentially improve outcomes in hundreds of thousands of people's lives using carbohydrate restriction illuminates a strategy to tap into thousands of years of human evolution.

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