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Narrative Review on Therapeutic Effects of Dietary Approach in Neurological Disorders

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ABSTRACT

Background: Since earlier times, humans have adjusted their diets to alleviate a variety of diseases, often with beneficial short- and long-term benefits. Diet was originally tried to treat and manage epilepsy in children in the late nineteenth century, with quite promising results. Finally, nutrition, fasting, and other dietary modifications have been utilized to help manage and treat numerous diseases such as cancer, diabetes, dyslipidemia, and rheumatic diseases, with often remarkable outcomes. As a result of these considerations, the objective of this research was to determine if diet and fasting strategies may be effectively used to treat neurological diseases.

Methods: The following electronic scientific resources were used in our analysis: PubMed, Google Scholar, Web of Science, and Science Direct. Between 1990 and 2022, appropriate English publications containing the phrases "fasting", "diet", "fasting mimicking diets", "fasting imitating diets", "ketogenic diet", "water-only fasting", "cerebral diseases", "fasting in neurodegenerative disorders" and "diets in neurodegenerative disorders" were located.

Results: Our findings indicate that dieting and fasting may be effective in treating and reducing the symptoms of neurological diseases, particularly in terms of lowered stress levels, which are important contributors to the symptomatology and pathophysiology of disorders. Numerous diseases have been linked to food. For example, caloric restriction has been shown to alleviate the severity of neurochemical imbalances, whereas intermittent fasting has been shown to protect neurons against malfunction and deterioration. Certain experimental studies have revealed that restricting food intake may enhance neurogenesis and synaptic plasticity in the nervous system.

Conclusion: In conclusion, the findings of this narrative review demonstrate that diets may be effectively adapted to neurological illnesses when the patient's current status, the severity of the disease, and the health status of the body are considered. In older individuals with serious neurological diseases, lighter diets with rigorous monitoring are indicated.

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INTRODUCTION

Brain disorders are one of the primary causes of mortality and disability globally, increasing more prevalent in recent years.[1-4] Although the vast amount of research launched to identify potential therapies for brain-correlated disorders, therapeutic choices remain mainly focused on symptom alleviation, whereas solutions are still to be discovered. Epidemiological research suggests that lifestyle variables may have a part in the prevention of brain-related disorders.[5, 6] For example, the relationship among nutrition and its influence on the brain.[7] Numerous diets have been proven to promote brain function, with the majority of data indicating the best advantages of a Mediterranean diet.[8]

While diets and calorie restriction have been shown to benefit brain function, they are difficult for many individuals to maintain over term and may have negative impacts on persons who have lower body mass index.[9, 10] Importantly, an increasing amount of available data from human and animal research suggests that fasting intervals without calorie or nutritional restriction may have comparable impacts on cognitive aspects and improve brain function.[11] Thus, in addition to the increased focus in the effect of dietary supply on cognition, there has been a significant focus in the time and frequency of eating as intermittent fasting, ketogenic diet, water-only fasting etc.

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Dietary therapies that induce coordinated improvements in the hematological and immunological systems, particularly in the intestinal microbiota, have a great potential for ameliorating and perhaps reversing Parkinson's disease.

Our investigation drew on the following electronic scientific resources: PubMed, Google Scholar, Web of Science, and Science Direct. Between 1990 and 2022, relevant English articles using the terms "fasting," "diet," "fasting mimicking diets," "ketogenic diet," "water-only fasting," "cerebral illnesses," "fasting in neurodegenerative disorders," and "diets in neurodegenerative disorders" were identified.

The studies were included in this review if they matched the following criteria: (1) Articles must be written in English; (2) Articles must be original papers, reviews, or case reports; (3) Patients involved in the studies must have been diagnosed with neurologic disorders; (4) There must be no external intervention during the study's experiment; (5) Neurologic patients must not have undergone a dieting or fasting procedure; and (6) Patients participating in the study must not have been diagnosed with dementia or psychiatric disorders.

The following studies were excluded: (1) studies having citations and patents; (2) studies published in a language other than English; (3) studies with abstracts but no data; and (4) studies using an alternative treatment other than dieting or fasting. The search results were processed, and the most relevant information is presented in this article as a narrative review.

Water-only fasting

In some studies, water-only fasting has been proven to prevent and aid cure intestinal inflammation.[12-14] Water-only fasting is a complete abstinence from food intake whilst ingesting unlimited amounts of water. This sort of fasting is considered to benefit health and may generate greater motivation for individuals to adopt a healthier dietary habits.[15, 16] This form of therapy was shown to induce physiological consequences that may be beneficial to health including increased ketogenesis, hormone action modulation, decreased inflammation and oxidative stress symptoms, lipolysis, and autophagy, as well as better physical and mental well-being.[17] The WF (water fasting) therapy is characterized by the use of a "no calories diet".[18, 19] A dverse effects of WF, could consist of elevated uric acid and creatinine serum levels, reduced glomerular filtration rate, or other major health issues.[20, 21] Ketosis is the metabolic product that occurs during the initial period of fasting. In the beginning phases of fasting, which is regarded as a moderate and sustainable condition, ketone bodies serve as an alternate fuel source for the neurons and other cells that are glucose-dependent.

After the initial phase, the level of ketones including b-hydroxybutyrate (b-HB) rises. They provide neuroprotective activity by enhancing mitochondrial respiration and thereby assuring adenosine triphosphate production.[22, 23] Additionally, ketones have been shown to increase the excitability of neuronal membranes and the incidence of autophagy, while decreasing inflammation and blocking free radical formation.[24] Acidosis, on either hand, accelerates the undesirable mechanism of calcium release from bones.[25] Additionally, ketones that remain in the body for a long length of time have been shown to protect or correct irregularities in the heart's energy homeostasis while fasting.[26] The negative of brief complete fasting is that osteogenesis indicators deteriorate. Nevertheless, the most visible effect of fasting or calorie restriction is loss of weight, which happens at both the fat-free mass and body fat levels.[27, 28]

It is advised that a person consume 2-3 litres of liquids everyday while undergoing WF, preferably mineralized water. This partly meets the body's requirements for maintaining equilibrium of certain minerals, considering that in some cases the minerals are better absorbed from liquids compared to solid food.[29, 30] On either side, the reduced water intake associated with WF, in the exclusion of nutrients provided by food, may result in substantial salt and potassium depletion from the body and the incidence of hypovolemia, endangering the health of those undergoing this form of approach. As a result, the levels of natrium, kalium and volemia must be evaluated to determine the medical state and safety of WF people.[18]

A week period of WF might be seen of as an acute sort of stress that boosts immunity, while prolonged stress hinders the body's capacity to mount a powerful immunological reaction.[31] One of the many additional consequences of fasting on the body, is therapeutic effect on neurological illnesses and also another being the autophagy stimulation.[32-34] Fasting's benefits are modulated by a number of situations, however it was demonstrated that improved mental agility, raised irritability, and enhanced thinking abilities in a sample of athletes.[35] Fasting, on the other hand, was shown to produce tiredness and lengthen reaction time in a two-choice response time test, diminish cognitive agility, and engage the hypothalamic-pituitary-adrenal axis in a sample of obese senior women.[36] Additionally, fasting lowered negative impact and resulted in symptom reduction in substance abusers.[37]

Ogodek's research[38] on 8 days of water fasting demonstrated decreased felt stress and preserved protein equilibrium in investigated men, as well as symptoms of dehydration, enhanced ketogenesis, hyponatremia, hypoglycemia, and hyperuricemia, as well as a considerable decrease in weight.

Fasting Imitating Diets

Numerous disorders are connected to diet. Caloric limitation, for instance, has been demonstrated to ameliorate the intensity of neurochemical imbalances and motor deficits in a primate prototype of Parkinson's disease,[39] and intermittent fasting has been demonstrated to protect neurons from dysfunction and degradation in rat models of Huntington's disease (40), but the pathway which involves such advantages is widely undefined.

While several studies utilized fasting as a nutritional therapy, extended water consumption is problematic for the general populace, especially the elderly, and its severe nature may exacerbate malnutrition and malfunction.[39-41] As a result, fasting imitating diets, which minimizes the costs associated with fasting, may be a more effective method for examining the influence of calorie restriction on neurodegenerative illnesses in the elderly.

The fasting imitating diet is usually divided into three 7-day phases, with every phase characterized by three days in a row

of fasting imitating diet followed by four consecutive days of self-willing eating.[41]

Intermittent fasting and fasting mimicking diets have been shown to be helpful in extending healthy longevity and treating a number of illnesses in mice models.[41-44] Fasting mimicking diets have the potential to lower the incidence of cancer and age-related immunosuppression/immunosenescence, a function that is helped by hematopoietic stem cell-based rejuvenation.[44-46] Additionally, fasting-mimicking diets cycles have been shown to alleviate or repair progression of the disease in animal models of multiple sclerosis, as well as both types of diabetes.[45, 46] Research has shown that a 24-hour fast has a beneficial impact on the intestinal stem cell activity of young and old mice through the fatty acid oxidation pathway.[47]

Fasting imitating diets induce comparable modifications in markers related to stress tolerance and lifespan as fasting does.[44] Three cycles of fasting simulating diets were chosen in a pilot clinical research to alter aging and cell protection indicators, including as IGF-I, IGFBP-1, glucose, and ketone bodies, as well as cardiovascular disease risk markers (decreased C-reactive protein levels).[44] Furthermore, a pilot clinical experiment found that three cycles of fasting imitation diets reduced risk factors for ageing process, diabetes, cardiovascular disease, and cancer without causing significant side effects,[48] indicating that fasting imitating diets may be used to enhance health and longevity. Fasting mimicking diets, in particular, are successful for inducing lineage reprogramming and insulin production in pancreatic cells for both healthy and type 1 diabetes subjects treated with serum from clinical trial participants.[45]

Fasting Imitating Diets in Parkinson's Disease

As is well documented, dietary changes including alternate-day fasting, 72–96-hour fasting, and time-restricted eating affect the structure of the intestinal microbiota.[49-52] Significant modifications in the makeup of the microbiota may have a direct effect on the microbiome's products, including short-chain fatty acids, trimethylamine N-oxide, tryptophan, and tyrosine derivatives.[53] The intestinal microbiota has a major effect on the brain, affecting behavior, neurotransmitter synthesis, microglial function, neurogenesis, and the function of the blood–brain barrier.[54] Research has lately shown that the gut microbiota has neuroprotective properties in PD rodents.[55-58]

Certain experimental research has demonstrated that food restriction may boost neurogenesis and synaptic plasticity in the nervous system.[59] Food limitation was demonstrated to decrease illness development in huntingtin-mutant mice by increasing the levels of brain-derived neurotrophic factor in the striatum and cortex.[40]

In the work, of Zhou et al.[60] was revealed that fast mimicking diet, which involves fasting three days in a week for three weeks, had significant neuroprotective benefits in PD mice in regain significant motor function and being protected against dopaminergic neuronal death in the nervous system. Brain-derived neurotrophic factor levels were elevated in PD mice, which is known to improve dopaminergic neuron lifespan and induced changes in the structure of the gut microbiota. Also, they have found that the gut microbiome has a role in the neuroprotection induced by the fasting imitating diets in PD.

The advantages of IF are most probably due to regulated levels of minor stress and recuperation, or hormesis.[39] IF has been shown to improve insulin sensitivity,[61] decrease excitotoxicity,[62] decrease neurodegeneration,[62] and protect from autonomic dysfunction,[63] as well as motor and cognitive deterioration, in PD models.64 IF ameliorates the other pathologic characteristics of Parkinson's disease[65] by promoting neurogenesis and increasing the survival of neural progenitors.[66] Additionally, the ensuing ketosis might support reduced excitotoxicity by increasing GABA levels.[67]

Notably, IF could be beneficial for non-motor symptoms of Parkinson's disease additional to motor symptoms. Griffioen et al., demonstrated that intermittent fasting resulted in a lowered alpha-synuclein burden in the brainstem, which makes a significant contribution to autonomic dysfunction (increased resting pulse rate, impaired cardiovascular stress reaction, and lowered parasympathetic activity) that is frequently observed in Parkinson's disease.[67] Due to the fact that autonomic dysfunction relates to decreased functional status, it continues to be a significant treatment focus additional to motor symptoms.[68, 69]

Kamel et al.[70] studied twenty-four Parkinson's disease patients who fasted throughout Ramadan and found no major negative effects. There were no substantial improvements in quality of life, non-motor symptom scale, or clinical perception of severity scale score following Ramadan.

Several clinical trials have been conducted to determine the effect of dietary treatments or supplements on mitochondrial dysfunction in Parkinson's disease. A 28-day ketogenic diet experiment in seven individuals with Parkinson's disease revealed variable degrees of compliance. Patients who completed the experiment, on the other hand, had a better Unified Parkinson's Disease Rating Scale (UPDRS) score, as well as improvements in motor symptoms, attitude, and energy level.[71] Amigo et al. demonstrated the viability of a ketogenic diet in PD patients by dividing them into two groups: one on a ketogenic diet and another on a reduced fat and increased carbohydrate diet.[65, 71] The groups improved from initial MDS-UPDRS Parts 1–4 scores; but the KD group improved much more than the control group, with higher improvements in non-motor, everyday experience ratings. These data corroborated the hypothesis that KD also alleviated non-motor PD symptoms.[65] Despite their small sample numbers and absence of confirming outcomes, these studies demonstrate the viability of food intervention in Parkinson's disease.

Parkinson's disease is an irreversible neurodegenerative condition characterized by alpha-synuclein buildup, mitochondrial dysfunction, and oxidative stress. Increasing mitochondrial activity and reducing oxidative stress may have favorable benefits on Parkinson's disease. IF may have a beneficial effect on the pathological mitochondrial modifications shown in Parkinson's disease. It is associated with fewer negative impacts and is less restrictive than other frequently used dietary therapies. Finally, IF could be used in conjunction with other therapies to combat pathophysiologic illness pathways and improve treatment efficacy.

In summary, the current study sheds new light on an unique therapeutic method for the treatment of Parkinson's disease.

Fast mimicking diet can restore motor function, ameliorate dopaminergic neuron decrease in the substantia nigra, and increase dopamine and serotonin levels in the basal ganglia of PD rodents. The mechanisms are linked to the adjustments of gut microbiota to regulate microbial dysbiosis.

Fasting in Myasthenia gravis

Ramadan fasting is a month-long period during which millions of Muslims withhold from eating and drink from sunrise to sunset. The study of Ismail et al., on the impact of Ramadan fasting on myasthenia gravis patients indicated that both patients with ocular MG and those with generalized MG had a positive outcome. Additionally, only 15.0% of their research sample had symptoms deteriorating, although no patient suffered respiratory dysfunction or myasthenic crisis.

Fasting and epilepsy

This study of Magdy et al., showed beneficial effects of Ramadan fasting on Muslim individuals suffering from focal, myoclonic, or absence seizures.

Intermittent fasting is a diet technique in which a person alternates between periods of fasting or calorie restriction and regular food intake over a set length of time.[72] Caloric restriction and intermittent fasting appear to offer a variety of good health impacts, such increased immune system performance, higher cognitive ability, and even decreased seizure occurrences in certain epileptic patients. Time-restricted feeding has been shown to be anticonvulsant, and this strict diet can produce alterations in energy metabolism and epigenetic changes.[73]

Ramadan is likely to bring about changes in the scheduling of antiepileptic medicines, disruptions in the circadian sleep cycle, and possibly lack of sleep.[74] These alterations to one's daily routine are well-documented possible causes for deteriorating seizure control.[75] Nevertheless, food regulation is one of the most ancient and widely used types of therapy for a wide variety of disorders. In the epilepsy case it is performed is for antiquity, considering that doctors have controlled epilepsy with dietary adjustments and limitations.

Fasting, in conjunction to the ketogenic diet, has a distinct effect in reprogramming metabolic and consequently stress tolerance networks.[17] Ramadan is a tough and difficult period of year due to the many elements related with fasting, including weariness, mental anguish, disrupted sleep pattern and length, and changes in medication consumption regimens (76). Fasting during Ramadan results in increased levels of many neurotrophins, including brain-derived neurotrophic factor and insulin-like growth factor-1.[77] Serum concentrations of BDNF and IGF-1 were shown to be significantly lower in individuals with focal seizures, with or without progression to bilateral tonic-clonic seizures and were appeared to be strongly linked with increased seizure recurrence.[78]

Epilepsy is a neurological disorder that is frequently persistent and needs many years of therapy.[79] Antiepileptic pharmaceutical therapy on a lengthy basis may occasionally interact with the patient's daily tasks due to the requirement to follow to a predetermined dose schedule and keep regular and adequate sleeping time. Fasting in Ramadan is comparable to what the literature refers to as time-restricted feeding, an eating habit that entails limiting food intake to specified periods of time of the day.[80] Islamic fasting is abstaining from eating, water, smoking, and oral drugs, from morning till night for one month.[80] Throughout Ramadan, regular meals and sleeping hours are often altered as a consequence of fasting for extended periods of the day. As a result, people with epilepsy who choose to fast throughout Ramadan may need to make major changes to their everyday routine, such as the scheduling of their prescriptions. Fasting, on the other hand, has been involved in the treatment of epileptic convulsions for many years. In 1911, Guelpa et al. published the first report on the use of fasting to control epilepsy.[81] They tested 20 individuals with epilepsy, both adults and children, using a technique termed "detoxification." The detoxification approach involves following a calorie-restricted plant-based diet with intermittent fasting and purge intervals.

In the majority of instances, this diet was exceedingly difficult to adhere to; also, some patients mislead doctors about their food intake. They produced outstanding outcomes given these setbacks.[81] Conklin described the first use of intermittent fasting to control epilepsy in 1922, with recovery rates as high as 50% in adults and 90% in juvenile sufferers.[82] According to Gamble of Johns Hopkins, the existence of a metabolic role in the genesis of epilepsy is clearly suggested.[83] Fasting was hypothesized to cure epilepsy through raising blood plasma acidity as a result of the ketosis effect.[84] Dr. Mynie Peterman of the Mayo Clinic presented the first systematic ketogenic diet as a therapy for epilepsy in 1924.[85] Since then, the ketogenic diet has been shown to be a successful therapy for epilepsy in both adults and children.[86-88] There are few studies on the impact of Ramadan fasting on epileptic sufferers. A review of the literature revealed just two observational studies. Al-Mahdawi et al. observed 35 patients who fasted an average of 12 hours each day.[89] They divided the patients into two groups based on their capacity to fast: those who "succeeded to fast Ramadan" and those who "failed to fast Ramadan."

At baseline, more over half of the subjects had not experienced a seizure in at approximately a year (before Ramadan). The authors discovered that individuals with epilepsy who had a normal neurological examination and electroencephalogram were more able to endure fasting than others. However, this research did not assess the prevalence of seizures or vulnerability to them during Ramadan.

Gomceli et al. investigated how Ramadan affected therapeutic strategies and seizure occurrence in individuals with epilepsy. A number of 114 patients were prospectively monitored every 3 months for at minimum one year prior to Ramadan and for the three months after Ramadan. At baseline, almost 50% of subjects reported having no convulsions in the year before fasting. During Ramadan, the authors observed a little increase in seizure frequency. This rise was linked to changes in the pharmacodynamics of antiepileptic drugs, and also modifications in sleep patterns and emotional stress.[76]

Ketogenic Diet

Both KDs and fasting diets (FDs) dramatically restrict carbohydrate consumption, but it has been claimed that the ensuing ketone bodies enhance demyelinated axon regeneration.[90] Therefore, it is possible that one of these

nutritional regimens might have therapeutic benefits in people with multiple sclerosis.

The KD was first developed to replicate the biochemical effects of fasting,[91] and was utilized as an alternate therapy for pharmacoresistant infantile epilepsy as early as the 1920s (92). Ever since, various neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease have been found to benefit from KDs.[93, 94]

In the context of MS, there is experimental data supporting the effectiveness of KDs and FDs using the known animal model of MS, experimental autoimmune encephalomyelitis (EAE). A KD reduced disease development, improved motor impairment and hippocampus atrophy, reversed lesions, and inhibited the production of inflammatory cytokines and reactive oxygen species.[95] A fasting-like diet was found to postpone illness initiation and progression. While fasting, this was associated with elevated cortisol levels levels, autoreactive lymphocyte apoptosis, and oligodendrocyte regeneration.[41] Other experimental autoimmune encephalomyelitis studies have shown the positive effects of intermittent fasting and chronic calorie restriction.[96-98]

Modifications in the intestinal bacteria have been related to a variety of disease states, particularly autoimmune disorders such as multiple sclerosis and the gut microbiota is inextricably tied to our immune response and inflammatory reactions.

Remarkably, new research indicates that gut dysbiosis may also develop in people with neurodegenerative disorders.[99-101] Both KDs and FDs may have a beneficial effect on the intestinal microbiota by increasing microbiome in the intestine.[101, 102]

Ketogenic Diet in Epilepsy

Fasting has been used to cure epilepsy since Hippocrates' time, and it was used to control epilepsy until the 1920s.103 The emergence of new antiepileptic drugs during the last several decades has changed the focus off from dietary therapy for epilepsy. The ketogenic diet was first developed to control epilepsy by inducing a ketosis state similar to that experienced in the time of fasting. The ketogenic diet has been shown to be a treatment option for drug-resistant epilepsy and is currently routinely used in children.[104, 105]

A ketogenic diet has traditionally been advised to treat epilepsy. The classic ketogenic diet is a high-fat, low-carbohydrate diet with caloric and hydration restrictions. The diet simulates fasting, causing the metabolism to shift to fat as the predominant source of energy. The breakdown of fatty acids inside the liver results in the formation of ketone bodies, which promotes ketosis in the urine.[106] Nevertheless, patients who are less receptive to the ketogenic diet can benefit from intermittent fasting, implying that intermittent fasting has a different effect on seizure management than the ketogenic diet.[107] The current research demonstrated that Ramadan fasting significantly improved some seizure types. Ramadan fasting could be comparable to KD and intermittent fasting in that it all improves management of focal and myoclonic seizures.[106, 107]

Fasting and ketogenic diet have a number of mechanisms in common that could aid in seizure management.[108] Following a fast, the human body undergoes a physiological condition known as ketosis, which is associated with decreased blood glucose, depleted liver glycogen reserves, and hepatic synthesis of fat-derived ketone bodies, which serves as a key production of fuel for the neurons (106). These ketone bodies, particularly beta-hydroxybutyrate, were discovered to have an anticonvulsant action directly.[109-111]

Ketogenic Diet and Alzheimer's Disease

Research indicated a possible effect of KD on the progression of Alzheimer's disease in people. Reger et al..[93] found that oral treatment of MCT increased plasma ketone bodies and may benefit cognitive performance in elderly adults with memory problems.

Henderson et al. [112] treated patients with mild to moderate AD with medium-chain triglycerides. The delivery of that kind of fatty acid resulted in a rise in blood ketone body levels and an improvement in cognitive performance.

On different days, Ota et al.[113] administered medium-chain triglycerides to twenty Japanese patients with mild-to-moderate AD. After eight weeks, patients demonstrated considerable improvement on both immediate and delayed logical memory tests when matched to their baseline score. They demonstrated considerable progress in the digit-symbol coding and instantaneous logical memory tests after 12 weeks as contrasted to baseline.

The Ketogenic Diet Retention and Feasibility Trial[114] observed 15 individuals with AD who followed a KD enhanced with MCTs. They discovered that when individuals attained total ketosis, the mean of the Alzheimer's Disease Assessment Scale cognitive subscale score enhanced considerably throughout the diet and then returned to baseline after a period.

Ooi and colleagues[115] discovered that a three-year periodic fasting diet improved cognitive performance in elderly adults with moderate cognitive decline when comparing to age-matched adults who practice periodic fasting seldom or to age-matched adults who do not follow periodic fasting.

Krikorian et al.[116] demonstrated that the concentrations of ketone bodies were favorably connected with cognitive function in Alzheimer's disease patients. The scientists concluded that even brief usage of a low-carbohydrate regimen may enhance cognitive performance in older persons at elevated risk of Alzheimer's disease.

Ketogenic Diet and Parkinson's Disease

Vanitallie et al.[61] conducted a clinical trial in which they examined five people with PD who volunteered to follow KD diets in their home contexts for 28 days. The investigators saw minor increase in the Unified Parkinson's Disease Rating Scale scores but could not rule out placebo effects. Phillips et al.[62] compared the effects of a low-fat vs a ketogenic diet on 47 Parkinson's disease patients over a two-month period. The diet had positive outcome motor and nonmotor symptoms considerably; nevertheless, the ketogenic group improved nonmotor symptoms much more.

CONCLUSION

In conclusion, our findings suggest that periods of FMD and refeeding might help alleviate or cure the symptoms and pathology related with Parkinson's disease, in particular

through modulating brain transmitters and the gut flora. While water-only fasting has certain benefits, fasting imitating diets, which decrease the expenses associated with fasting, may be a more effective strategy for investigating the impact of calorie restriction on neurology disorders, especially neurodegenerative diseases in the elderly patients.

REFERENCES

1. Castillo X, Castro-Obregón S, Gutiérrez-Becker B, Gutiérrez-Ospina G, Karalis N, Khalil AA, et al. Re-thinking the etiological framework of neurodegeneration. Front Neurosci 2019;13:728. https://doi.org/10.3389/fnins.2019.00728.
2. Feigin VL, Abajobir AA, Abate KH, Abd-Allah F, Abdulle AM, Abera SF, et al. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol 2017;16:877–97. https://doi.org/10.1016/s1474-4422(17)30299-5.
3. Gogu AE, Pusztai A, Stroe AZ, Docu Axelerad D, Docu Axelerad A. Back pain in rare diseases: A comparison of neck and back pain between spinal cord ischemia and spinal Dural arteriovenous fistula. Brain Sci 2020;10:618. https://doi.org/10.3390/brainsci10090618.
4. Chita DS, Tudor A, Christodorescu R, Buleu FN, Sosdean R, Deme SM, et al. MTHFR gene polymorphisms prevalence and cardiovascular risk factors involved in cardioembolic stroke type and severity. Brain Sci 2020;10:476. https://doi.org/10.3390/brainsci10080476.
5. Solfrizzi V, Capurso C, D'Introno A, Colacicco AM, Santamato A, Ranieri M, et al. Lifestyle-related factors in predementia and dementia syndromes. Expert Rev Neurother 2008;8:133–58. https://doi.org/10.1586/14737175.8.1.133.
6. Budisteanu M, Andrei E, Linca F, Hulea DS, Velicu AC, Mihailescu I, et al. Predictive factors in early onset schizophrenia. Exp Ther Med 2020;20:210. https://doi.org/10.3892/etm.2020.9340.
7. Moore K, Hughes CF, Ward M, Hoey L, McNulty H. Diet, nutrition and the ageing brain: current evidence and new directions. Proc Nutr Soc 2018;77:152–63. https://doi.org/10.1017/s0029665117004177.
8. Martínez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvadó J, San Julián B, et al. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. J Neurol Neurosurg Psychiatry 2013;84:1318–25. https://doi.org/10.1136/jnnp-2012-304792.
9. Vitousek KM. The case for semi-starvation. Eur Eat Disord Rev 2004;12:275–8. https://doi.org/10.1002/erv.593.
10. Normandin E, Houston DK, Nicklas BJ. Caloric restriction for treatment of geriatric obesity: Do the benefits outweigh the risks? Curr Nutr Rep 2015;4:143–55. https://doi.org/10.1007/s13668-015-0123-9.
11. Mattson MP, Moehl K, Ghena N, Schmaedick M, Cheng A. Intermittent metabolic switching, neuroplasticity and brain health. Nat Rev Neurosci 2018;19:63–80. https://doi.org/10.1038/nrn.2017.156.
12. Okada T, Otsubo T, Hagiwara T, Inazuka F, Kobayashi E, Fukuda S, et al. Intermittent fasting prompted recovery from dextran sulfate sodium-induced colitis in mice. J Clin Biochem Nutr 2017;61:100–7. https://doi.org/10.3164/jcbn.17-9.
13. Sävendahl L, Underwood LE, Haldeman KM, Ulshen MH, Lund PK. Fasting prevents experimental murine colitis produced by dextran sulfate sodium and decreases interleukin-1 beta and insulin-like growth factor I messenger ribonucleic acid. Endocrinology 1997;138:734–40. https://doi.org/10.1210/endo.138.2.4941.
14. Any DA, Daniel DA. Comparative evaluation of pregabaline, gabapentine, sertraline and duloxetine in painful diabetic non insulin-dependent neuropathy. Procedia Soc Behav Sci 2015;191:469–72. https://doi.org/10.1016/j.sbspro.2015.04.271.
15. Ismail S, Manaf RA, Mahmud A. Comparison of time-restricted feeding and Islamic fasting: a scoping review. East Mediterr Health J 2019;25:239–45. https://doi.org/10.26719/emhj.19.011.
16. Bonjour M, Gabriel S, Goldhamer AC, Myers TR. Medically supervised, water-only fasting followed by a whole-plant-food diet reduces visceral adipose tissue. Ijdrp 2021;3. https://doi.org/10.22230/ijdrp.2021v3n2a267.
17. Longo VD, Mattson MP. Fasting: Molecular mechanisms and clinical applications. Cell Metab 2014;19:181–92. https://doi.org/10.1016/j.cmet.2013.12.008.
18. Wilhelmi de Toledo F, Grundler F, Bergouignan A, Drinda S, Michalsen A. Safety, health improvement and well-being during a 4 to 21-day fasting period in an observational study including 1422 subjects. PLoS One 2019;14:e0209353. https://doi.org/10.1371/journal.pone.0209353.
19. Tripolt NJ, Stekovic S, Aberer F, Url J, Pferschy PN, Schröder S, et al. Intermittent fasting (alternate day fasting) in healthy, non-obese adults: Protocol for a cohort trial with an embedded randomized controlled pilot trial. Adv Ther 2018;35:1265–83. https://doi.org/10.1007/s12325-018-0746-5.
20. Mojto V, Gvozdjakova A, Kucharska J, Rausova Z, Vancova O, Valuch J. Effects of complete water fasting and regeneration diet on kidney function, oxidative stress and antioxidants. Bratisl Lek Listy 2018;119:107–11. https://doi.org/10.4149/bll_2018_020.
21. Wuensch T, Quint J, Mueller V, Mueller A, Wizenty J, Kaffarnik M, et al. Identification of serological markers for pre- and postoperative fasting periods. Clin Nutr ESPEN 2019;30:131–7. https://doi.org/10.1016/j.clnesp.2019.01.004.
22. Newman JC, Verdin E. B-hydroxybutyrate: Much more than a metabolite. Diabetes Res Clin Pract 2014;106:173–81. https://doi.org/10.1016/j.diabres.2014.08.009.
23. Charunyanont Y, Tubtimrattana A, Tansrisawad N, Thirati P. Effect of body refrigeration on the postmortem formation of gamma hydroxybutyrate in whole blood. Forensic Sci Int 2022;334:111247. https://doi.org/10.1016/j.forsciint.2022.111247.
24. Alirezaei M, Kemball CC, Flynn CT, Wood MR, Whitton JL, Kiosses WB. Short-term fasting induces profound neuronal autophagy. Autophagy 2010;6:702–10. https://doi.org/10.4161/auto.6.6.12376.
25. Klein-Nulend J, Veldhuijzen JP, de Jong M, Burger EH. Increased bone formation and decreased bone resorption in fetal mouse calvaria as a result of intermittent compressive force in vitro. Bone Miner 1987;2:441–8.
26. Horton JL, Davidson MT, Kurishima C, Vega RB, Powers JC, Matsuura TR, et al. The failing heart utilizes 3-hydroxybutyrate as a metabolic stress defense. JCI Insight 2019;4. https://doi.org/10.1172/jci.insight.124079.
27. Müller MJ, Enderle J, Pourhassan M, Braun W, Eggeling B, Lagerpusch M, et al. Metabolic adaptation to caloric restriction and subsequent refeeding: the Minnesota Starvation Experiment revisited. Am J Clin Nutr 2015;102:807–19. https://doi.org/10.3945/ajcn.115.109173.
28. Tinsley GM, La Bounty PM. Effects of intermittent fasting on body composition and clinical health markers in humans. Nutr Rev 2015;73:661–74. https://doi.org/10.1093/nutrit/nuv041.
29. Vitoria I, Maraver F, Ferreira-Pêgo C, Armijo F, Moreno Aznar L, Salas-Salvadó J. The calcium concentration of public drinking waters and bottled mineral waters in Spain and its contribution to satisfying nutritional needs. Nutr Hosp 2014;30:188–99. https://doi.org/10.3305/nh.2014.30.1.7491.
30. Greupner T, Schneider I, Hahn A. Calcium bioavailability from mineral waters with different mineralization in comparison to milk and a supplement. J Am Coll Nutr 2017;36:386–90. https://doi.org/10.1080/07315724.2017.1299651.
31. Dragoş D, Tănăsescu MD. The effect of stress on the defense systems. J Med Life 2010;3:10–8.
32. Sirbu CA, Ghinescu MC, Axelerad AD, Sirbu AM, Ionita-Radu F. A new era for monoclonal antibodies with applications in neurology (Review). Exp Ther Med 2021;21:86. https://doi.org/10.3892/etm.2020.9519.
33. Docu Axelerad A, Stroe AZ, Gogu AE, Docu Axelerad D. Assessing the values of circulating immune complexes in multiple sclerosis patients following immunomodulator or corticosteroid treatment. Exp Ther Med 2021;21:542. https://doi.org/10.3892/etm.2021.9974.
34. Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes. Ageing Res Rev 2017;39:46–58. https://doi.org/10.1016/j.arr.2016.10.005.

35. Solianik R, Sujeta A, Terentjevienė A, Skurvydas A. Effect of 48 h fasting on autonomic function, brain activity, cognition, and mood in amateur weight lifters. Biomed Res Int 2016;2016:1503956. https://doi.org/10.1155/2016/1503956.
36. Solianik R, Žlibinaitė L, Drozdova-Statkevičienė M, Sujeta A. Forty-eight-hour fasting declines mental flexibility but improves balance in overweight and obese older women. Physiol Behav 2020;223:112995. https://doi.org/10.1016/j.physbeh.2020.112995.
37. Nakajima M, al'Absi M. Influences of fasting on stress response and withdrawal symptoms in habitual khat users. Eur Addict Res 2021;27:49–57. https://doi.org/10.1159/000506737.
38. Ogłodek E, Pilis Prof W. Is water-only fasting safe? Glob Adv Health Med 2021;10:21649561211031176. https://doi.org/10.1177/21649561211031178.
39. Maswood N, Young J, Tilmont E, Zhang Z, Gash DM, Gerhardt GA, et al. Caloric restriction increases neurotrophic factor levels and attenuates neurochemical and behavioral deficits in a primate model of Parkinson's disease. Proc Natl Acad Sci U S A 2004;101:18171–6. https://doi.org/10.1073/pnas.0405831102.
40. Duan W, Guo Z, Jiang H, Ware M, Li X-J, Mattson MP. Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice. Proc Natl Acad Sci U S A 2003;100:2911–6. https://doi.org/10.1073/pnas.0536856100.
41. Choi IY, Piccio L, Childress P, Bollman B, Ghosh A, Brandhorst S, et al. A diet mimicking fasting promotes regeneration and reduces autoimmunity and multiple sclerosis symptoms. Cell Rep 2016;15:2136–46. https://doi.org/10.1016/j.celrep.2016.05.009.
42. Choi IY, Lee C, Longo VD. Nutrition and fasting mimicking diets in the prevention and treatment of autoimmune diseases and immunosenescence. Mol Cell Endocrinol 2017;455:4–12. https://doi.org/10.1016/j.mce.2017.01.042.
43. Lee C, Longo V. Dietary restriction with and without caloric restriction for healthy aging. F1000Res 2016;5:117. https://doi.org/10.12688/f1000research.7136.1.
44. Brandhorst S, Choi IY, Wei M, Cheng CW, Sedrakyan S, Navarrete G, et al. A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan. Cell Metab 2015;22:86–99. https://doi.org/10.1016/j.cmet.2015.05.012.
45. Cheng C-W, Adams GB, Perin L, Wei M, Zhou X, Lam BS, et al. Prolonged fasting reduces IGF-1/PKA to promote hematopoietic-stem-cell-based regeneration and reverse immunosuppression. Cell Stem Cell 2016;18:291–2. https://doi.org/10.1016/j.stem.2016.01.018.
46. Cheng C-W, Villani V, Buono R, Wei M, Kumar S, Yilmaz OH, et al. Fasting-mimicking diet promotes Ngn3-driven ß-cell regeneration to reverse diabetes. Cell 2017;168:775-788.e12. https://doi.org/10.1016/j.cell.2017.01.040.
47. Mihaylova MM, Cheng C-W, Cao AQ, Tripathi S, Mana MD, Bauer-Rowe KE, et al. Fasting activates fatty acid oxidation to enhance intestinal stem cell function during homeostasis and aging. Cell Stem Cell 2018;22:769-778.e4. https://doi.org/10.1016/j.stem.2018.04.001.
48. Wei M, Brandhorst S, Shelehchi M, Mirzaei H, Cheng CW, Budniak J, et al. Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease. Sci Transl Med 2017;9:eaai8700. https://doi.org/10.1126/scitranslmed.aai8700.
49. Deitch EA, Winterton J, Berg R. Effect of starvation, malnutrition, and trauma on the gastrointestinal tract flora and bacterial translocation. Arch Surg 1987;122:1019–24. https://doi.org/10.1001/archsurg.1987.01400210057008.
50. Sonoyama K, Fujiwara R, Takemura N, Ogasawara T, Watanabe J, Ito H, et al. Response of gut microbiota to fasting and hibernation in Syrian hamsters. Appl Environ Microbiol 2009;75:6451–6. https://doi.org/10.1128/AEM.00692-09.
51. Li G, Xie C, Lu S, Nichols RG, Tian Y, Li L, et al. Intermittent fasting promotes white adipose browning and decreases obesity by shaping the gut Microbiota. Cell Metab 2017;26:672-685.e4. https://doi.org/10.1016/j.cmet.2017.08.019.
52. Zarrinpar A, Chaix A, Yooseph S, Panda S. Diet and feeding pattern affect the diurnal dynamics of the gut microbiome. Cell Metab 2014;20:1006–17. https://doi.org/10.1016/j.cmet.2014.11.008.
53. Zhang LS, Davies SS. Microbial metabolism of dietary components to bioactive metabolites: opportunities for new therapeutic interventions. Genome Med 2016;8:46. https://doi.org/10.1186/s13073-016-0296-x.
54. Luczynski P, McVey Neufeld K-A, Oriach CS, Clarke G, Dinan TG, Cryan JF. Growing up in a bubble: Using germ-free animals to assess the influence of the gut Microbiota on brain and behavior. Int J Neuropsychopharmacol 2016;19. https://doi.org/10.1093/ijnp/pyw020.
55. Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, et al. Gut Microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell 2016;167:1469-1480.e12. https://doi.org/10.1016/j.cell.2016.11.018.
56. Qian Y, Yang X, Xu S, Wu C, Song Y, Qin N, et al. Alteration of the fecal microbiota in Chinese patients with Parkinson's disease. Brain Behav Immun 2018;70:194–202. https://doi.org/10.1016/j.bbi.2018.02.016.
57. Yang X, Qian Y, Xu S, Song Y, Xiao Q. Longitudinal analysis of fecal microbiome and pathologic processes in a rotenone induced mice model of Parkinson's disease. Front Aging Neurosci 2017;9:441. https://doi.org/10.3389/fnagi.2017.00441.
58. Torres ERS, Akinyeke T, Stagaman K, Duvoisin RM, Meshul CK, Sharpton TJ, et al. Effects of sub-chronic MPTP exposure on behavioral and cognitive performance and the microbiome of wild-type and mGlu8 knockout female and male mice. Front Behav Neurosci 2018;12:140. https://doi.org/10.3389/fnbeh.2018.00140.
59. Mattson MP, Duan W, Guo Z. Meal size and frequency affect neuronal plasticity and vulnerability to disease: cellular and molecular mechanisms: Meal size and frequency affects neuronal plasticity. J Neurochem 2003;84:417–31. https://doi.org/10.1046/j.1471-4159.2003.01586.x.
60. Zhou Z-L, Jia X-B, Sun M-F, Zhu Y-L, Qiao C-M, Zhang B-P, et al. Neuroprotection of fasting mimicking diet on MPTP-induced Parkinson's disease mice via gut Microbiota and metabolites. Neurotherapeutics 2019;16:741–60. https://doi.org/10.1007/s13311-019-00719-2.
61. Vanitallie TB, Nonas C, Di Rocco A, Boyar K, Hyams K, Heymsfield SB. Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study. Neurology 2005;64:728–30. https://doi.org/10.1212/01.WNL.0000152046.11390.45.
62. Phillips MCL, Murtagh DKJ, Gilbertson LJ, Asztely FJS, Lynch CDP. Low-fat versus ketogenic diet in Parkinson's disease: A pilot randomized controlled trial: Low-Fat Versus Ketogenic Diet in PD. Mov Disord 2018;33:1306–14. https://doi.org/10.1002/mds.27390.
63. Mattson MP, Calabrese EJ. Hormesis: What it is and Why it Matters. Hormesis, Totowa, NJ: Humana Press; 2010, p. 1–13.
64. Anson RM, Guo Z, de Cabo R, Iyun T, Rios M, Hagepanos A, et al. Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake. Proc Natl Acad Sci U S A 2003;100:6216–20. https://doi.org/10.1073/pnas.1035720100.
65. Amigo I, Menezes-Filho SL, Luévano-Martínez LA, Chausse B, Kowaltowski AJ. Caloric restriction increases brain mitochondrial calcium retention capacity and protects against excitotoxicity. Aging Cell 2017;16:73–81. https://doi.org/10.1111/acel.12527.
66. Bayliss JA, Andrews ZB. Ghrelin is the metabolic link connecting calorie restriction to neuroprotection. Neural Regen Res 2016;11:1228–9. https://doi.org/10.4103/1673-5374.189171.
67. Griffioen KJ, Rothman SM, Ladenheim B, Wan R, Vranis N, Hutchison E, et al. Dietary energy intake modifies brainstem autonomic dysfunction caused by mutant α-synuclein. Neurobiol Aging 2013;34:928–35. https://doi.org/10.1016/j.neurobiolaging.2012.07.008.
68. Cersosimo MG, Benarroch EE. Autonomic involvement in Parkinson's disease: pathology, pathophysiology, clinical features and possible peripheral biomarkers. J Neurol Sci 2012;313:57–63. https://doi.org/10.1016/j.jns.2011.09.030.

69. Palma J-A, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies: TREATMENT OF AUTONOMIC DYSFUNCTION IN PD. Mov Disord 2018;33:372–90. https://doi.org/10.1002/mds.27344.
70. Kamel WA, Al Hashel JY, Damier P. How do Parkinson's disease patients manage Ramadan fasting? An observational study. Rev Neurol (Paris) 2019;175:560–3. https://doi.org/10.1016/j.neurol.2018.12.008.
71. Singh R, Lakhanpal D, Kumar S, Sharma S, Kataria H, Kaur M, et al. Late-onset intermittent fasting dietary restriction as a potential intervention to retard age-associated brain function impairments in male rats. Age (Dordr) 2012;34:917–33. https://doi.org/10.1007/s11357-011-9289-2.
72. Collier R. Intermittent fasting: the science of going without. CMAJ 2013;185:E363-4. https://doi.org/10.1503/cmaj.109-4451.
73. Landgrave-Gómez J, Mercado-Gómez OF, Vázquez-García M, Rodríguez-Molina V, Córdova-Dávalos L, Arriaga-Ávila V, et al. Anticonvulsant effect of time-restricted feeding in a pilocarpine-induced seizure model: Metabolic and epigenetic implications. Front Cell Neurosci 2016;10:7. https://doi.org/10.3389/fncel.2016.00007.
74. BaHammam A, Alrajeh M, Albabtain M, Bahammam S, Sharif M. Circadian pattern of sleep, energy expenditure, and body temperature of young healthy men during the intermittent fasting of Ramadan. Appetite 2010;54:426–9. https://doi.org/10.1016/j.appet.2010.01.011.
75. Hanke JM, Schindler KA, Seiler A. On the relationships between epilepsy, sleep, and Alzheimer's disease: A narrative review. Epilepsy Behav 2022;129:108609. https://doi.org/10.1016/j.yebeh.2022.108609.
76. Gomceli YB, Kutlu G, Cavdar L, Inan LE. Does the seizure frequency increase in Ramadan? Seizure 2008;17:671–6. https://doi.org/10.1016/j.seizure.2008.03.008.
77. Bastani A, Rajabi S, Kianimarkani F. The effects of fasting during Ramadan on the concentration of serotonin, dopamine, brain-derived neurotrophic factor and nerve growth factor. Neurol Int 2017;9:7043. https://doi.org/10.4081/ni.2017.7043.
78. Chen S-F, Jou S-B, Chen N-C, Chuang H-Y, Huang C-R, Tsai M-H, et al. Serum levels of brain-derived neurotrophic factor and insulin-like growth factor 1 are associated with autonomic dysfunction and impaired cerebral autoregulation in patients with epilepsy. Front Neurol 2018;9:969. https://doi.org/10.3389/fneur.2018.00969.
79. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55:475–82. https://doi.org/10.1111/epi.12550.
80. Anton SD, Moehl K, Donahoo WT, Marosi K, Lee SA, Mainous AG III, et al. Flipping the metabolic switch: Understanding and applying the health benefits of fasting: Flipping the metabolic switch. Obesity (Silver Spring) 2018;26:254–68. https://doi.org/10.1002/oby.22065.
81. Höhn S, Dozières-Puyravel B, Auvin S. History of dietary treatment: Guelpa & Marie first report of intermittent fasting for epilepsy in 1911. Epilepsy Behav 2019;94:277–80. https://doi.org/10.1016/j.yebeh.2019.03.018.
82. Haddad N, Melikyan G, Al Hail H, Al Jurdi A, Aqeel F, Elzafarany A, et al. Epilepsy in Qatar: Causes, treatment, and outcome. Epilepsy Behav 2016;63:98–102. https://doi.org/10.1016/j.yebeh.2016.07.043.
83. Gamble JL, Ross GS, Tisdall FF. The metabolism of fixed base during fasting. J Biol Chem 1923;57:633–95. https://doi.org/10.1016/s0021-9258(18)85480-1.
84. Wilder RM, Winter MD. The threshold of ketogenesis. J Biol Chem 1922;52:393–401. https://doi.org/10.1016/s0021-9258(18)85833-1.
85. Peterman MG. The ketogenic diet in the treatment of epilepsy: A preliminary report. Am J Dis Child 1924;28:28. https://doi.org/10.1001/archpedi.1924.04120190031004.
86. Nei M, Ngo L, Sirven JI, Sperling MR. Ketogenic diet in adolescents and adults with epilepsy. Seizure 2014;23:439–42. https://doi.org/10.1016/j.seizure.2014.02.015.
87. Klein P, Janousek J, Barber A, Weissberger R. Ketogenic diet treatment in adults with refractory epilepsy. Epilepsy Behav 2010;19:575–9. https://doi.org/10.1016/j.yebeh.2010.09.016.
88. Tyrlikova I, Klein P. Ketogenic diet treatment in adults with refractory epilepsy. Bioactive Nutraceuticals and Dietary Supplements in Neurological and Brain Disease, Elsevier; 2015, p. 433–9.
89. Al-Mahdawi AM. Epilepsy and Ramadan fasting. Neurosciences (Riyadh) 2002;7:207–9.
90. Storoni M, Plant GT. The therapeutic potential of the ketogenic diet in treating progressive multiple sclerosis. Mult Scler Int 2015;2015:681289. https://doi.org/10.1155/2015/681289.
91. Kossoff EH. More fat and fewer seizures: dietary therapies for epilepsy. Lancet Neurol 2004;3:415–20. https://doi.org/10.1016/S1474-4422(04)00807-5.
92. Winesett SP, Bessone SK, Kossoff EHW. The ketogenic diet in pharmacoresistant childhood epilepsy. Expert Rev Neurother 2015;15:621–8. https://doi.org/10.1586/14737175.2015.1044982.
93. Reger MA, Henderson ST, Hale C, Cholerton B, Baker LD, Watson GS, et al. Effects of beta-hydroxybutyrate on cognition in memory-impaired adults. Neurobiol Aging 2004;25:311–4. https://doi.org/10.1016/S0197-4580(03)00087-3.
94. Jabre MG, Bejjani B-PW. Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study. Neurology 2006;66:617; author reply 617. https://doi.org/10.1212/01.wnl.0000216108.57529.b1.
95. Kim DY, Hao J, Liu R, Turner G, Shi F-D, Rho JM. Inflammation-mediated memory dysfunction and effects of a ketogenic diet in a murine model of multiple sclerosis. PLoS One 2012;7:e35476. https://doi.org/10.1371/journal.pone.0035476.
96. Piccio L, Stark JL, Cross AH. Chronic calorie restriction attenuates experimental autoimmune encephalomyelitis. J Leukoc Biol 2008;84:940–8. https://doi.org/10.1189/jlb.0208133.
97. Kafami L, Raza M, Razavi A, Mirshafiey A, Movahedian M, Khorramizadeh MR. Intermittent feeding attenuates clinical course of experimental autoimmune encephalomyelitis in C57BL/6 mice. Avicenna J Med Biotechnol 2010;2:47–52.
98. Razeghi Jahromi S, Ghaemi A, Alizadeh A, Sabetghadam F, Moradi Tabriz H, Togha M. Effects of intermittent fasting on experimental autoimune encephalomyelitis in C57BL/6 mice. Iran J Allergy Asthma Immunol 2016;15:212–9.
99. Miyake S, Kim S, Suda W, Oshima K, Nakamura M, Matsuoka T, et al. Dysbiosis in the gut Microbiota of patients with multiple sclerosis, with a striking depletion of species belonging to Clostridia XIVa and IV clusters. PLoS One 2015;10:e0137429. https://doi.org/10.1371/journal.pone.0137429.
100. Chen J, Chia N, Kalari KR, Yao JZ, Novotna M, Paz Soldan MM, et al. Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls. Sci Rep 2016;6. https://doi.org/10.1038/srep28484.
101. Swidsinski A, Dörffel Y, Loening-Baucke V, Gille C, Göktas Ö, Reißhauer A, et al. Reduced mass and diversity of the colonic microbiome in patients with multiple sclerosis and their improvement with ketogenic diet. Front Microbiol 2017;8:1141. https://doi.org/10.3389/fmicb.2017.01141.
102. Cignarella F, Cantoni C, Ghezzi L, Salter A, Dorsett Y, Chen L, et al. Intermittent fasting confers protection in CNS autoimmunity by altering the gut Microbiota. Cell Metab 2018;27:1222-1235.e6. https://doi.org/10.1016/j.cmet.2018.05.006.
103. Bailey EE, Pfeifer HH, Thiele EA. The use of diet in the treatment of epilepsy. Epilepsy Behav 2005;6:4–8. https://doi.org/10.1016/j.yebeh.2004.10.006.
104. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol 2008;7:500–6. https://doi.org/10.1016/S1474-4422(08)70092-9.
105. Covey C. Ketogenic diets for drug-resistant epilepsy. Am Fam Physician 2021;103:524–5.

106. D'Andrea Meira I, Romão TT, Pires do Prado HJ, Krüger LT, Pires MEP, da Conceição PO. Ketogenic Diet and epilepsy: What we know so far. Front Neurosci 2019;13:5. https://doi.org/10.3389/fnins.2019.00005.

107. Hartman AL, Rubenstein JE, Kossoff EH. Intermittent fasting: a "new" historical strategy for controlling seizures? Epilepsy Res 2013;104:275–9. https://doi.org/10.1016/j.eplepsyres.2012.10.011.

108. Phillips MCL. Fasting as a therapy in neurological disease. Nutrients 2019;11:2501. https://doi.org/10.3390/nu11102501.

109. Vellucci SV, Webster RA. The effects of beta-carboline carboxylic acid ethyl ester and its free acid, administered ICV, on the anticonvulsant activity of diazepam and sodium valproate in the mouse. Pharmacol Biochem Behav 1986;24:823–7. https://doi.org/10.1016/0091-3057(86)90418-1.

110. Sirbu CA, Florea AA, Ghinescu MC, Docu-Axelerad A, Sirbu AM, Bratu OG, et al. Vaccination in multiple sclerosis - Challenging practices (Review). Exp Ther Med 2020;20:217. https://doi.org/10.3892/etm.2020.9347.

111. Docu Axelerad A, Stroe AZ, Gogu AE, Pusztai A, Jianu DC, Daniel D, et al. Clinical spectrum of symptoms in cerebral Toxocariasis (Review). Exp Ther Med 2021;21:521. https://doi.org/10.3892/etm.2021.9953.

112. Henderson ST, Vogel JL, Barr LJ, Garvin F, Jones JJ, Costantini LC. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. Nutr Metab (Lond) 2009;6:31. https://doi.org/10.1186/1743-7075-6-31.

113. Ota M, Matsuo J, Ishida I, Takano H, Yokoi Y, Hori H, et al. Effects of a medium-chain triglyceride-based ketogenic formula on cognitive function in patients with mild-to-moderate Alzheimer's disease. Neurosci Lett 2019;690:232–6. https://doi.org/10.1016/j.neulet.2018.10.048.

114. Taylor MK, Sullivan DK, Mahnken JD, Burns JM, Swerdlow RH. Feasibility and efficacy data from a ketogenic diet intervention in Alzheimer's disease. Alzheimers Dement (N Y) 2018;4:28–36. https://doi.org/10.1016/j.trci.2017.11.002.

115. Ooi TC, Meramat A, Rajab NF, Shahar S, Ismail IS, Azam AA, et al. Intermittent fasting enhanced the cognitive function in older adults with mild cognitive impairment by inducing biochemical and metabolic changes: A 3-year progressive study. Nutrients 2020;12:2644. https://doi.org/10.3390/nu12092644.

116. Krikorian R, Shidler MD, Dangelo K, Couch SC, Benoit SC, Clegg DJ. Dietary ketosis enhances memory in mild cognitive impairment. Neurobiol Aging 2012;33:425.e19-27. https://doi.org/10.1016/j.neurobiolaging.2010.10.006.