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Article

Role of Ketogenic Diets and Intermittent Fasting in Neurologic Diseases, Cancers and Obesity—A Comprehensive Review of Human Studies

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Abstract: Non-pharmacologic options like the ketogenic diet (KD) and intermittent fasting (IF) are practical nutritional interventions with minor reported side effects like gastrointestinal symptoms, dyslipidemia, and hypomagnesemia for various medical ailments. In conjunction with IF, KD shows promise in weight loss, diabetes management, cardiovascular disorders, polycystic ovarian syndrome, cancer, and chronic neurological disorders. Based on prior research, we have examined the mechanism of action of KD and IF and their effect on neurological diseases, cancer, and obesity. We have also suggested evidence-based recommendations for the safer practice of KD and IF. Despite potential benefits, long-term adherence to KD poses challenges. Periodic KD implementation may thus benefit newly diagnosed overweight or obese patients with type 2 diabetes mellitus, aiding blood glucose and lipid management while promoting weight loss. KD is a high-fat and low-carbohydrate diet with a ratio of fat to carbohydrates and protein being 4:1 or

3:1, and thus, for peripheral tissues and the brain, fatty acids become the mandatory source of cellular energy. Ketone bodies have been used as the primary energy source during fasting. KD has been utilized as an effective treatment for refractory epilepsy since the 1920s. Evidence of the neuroprotective role of KD in diseases like epilepsy, stroke, traumatic brain injury, Alzheimer's disease, and other neurological diseases has been noted. Since the 1960s, KD has become a popular method for obesity treatment. In addition, KD has been suggested as a potent anticancer therapy when used alone or as an adjuvant. KD may increase tumor cell sensitivity when combined with classic chemotherapy and radiotherapy. Thus, the probability that modifying the diet can help manage obesity, cancer, and chronic neurological disease without depending on pharmacological treatment and their serious side effects for a lifetime is promising and requires further investigation. KD holds promise as a potential adjunctive therapy in various neurological disorders, offering new avenues for treatment and neuroprotection. IF has shown potential in slowing the progression of neurodegenerative diseases such as Alzheimer's and Parkinson's by promoting antioxidant defense and suppressing inflammation. KD and IF show promise in cancer therapy by targeting altered cancer cell metabolism. Additionally, KD may enhance the effects of standard treatments like chemotherapy and radiotherapy. Some of the most robust reports of keto's possible benefits have come from glioblastoma, a very aggressive brain cancer. KD has also shown strong evidence for its effectiveness in weight loss, mainly attributed to its appetite-suppressing action in ketosis. However, long-term adherence to KD can be challenging, and periodic KDs may help manage blood glucose and lipid levels in overweight or obese patients with type 2 diabetes mellitus. Likewise, IF may be more effective than regular calorie restriction for achieving weight loss goals when combined with exercise programs. More prospective human studies are warranted to evaluate both KD and IF's potential therapeutic effectiveness and safety.

Keywords: ketogenic diet; intermittent fasting; neurological disorders; stroke; epilepsy; traumatic brain injury; headache; Alzheimer's disease; behavioral disease; cancer; obesity

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Introduction

In the United States, nearly 100 million Americans are affected by one of more than 1,000 neurological diseases. The US's current annual economic burden of common neurological diseases is nearly 800 billion dollars. Additionally, the cost is expected to double by the year 2050 due to the rise in the elderly population and the subsequent rise in the incidence of neurological diseases. (Gooch et al., 2017) In the breakdown of both direct (medical) and indirect (non-medical) costs, it was found that conditions such as Alzheimer's disease, dementia, chronic low back pain, stroke, traumatic brain injury (TBI), migraine headaches, epilepsy, multiple sclerosis, and Parkinson's disease had the highest annual expenditure. (Gooch et al., 2017) Strong evidence supports the average increase of 150-300 calories per day in the past 30 years, leading to more obesity and cardiovascular events in the US with no change in physical activity. (Johnson et al., 2009) Although many pharmacological methods could be controlled by neurological and other medical conditions, non-pharmacologic options such as exercise, mindfulness and meditation, and various diet plans are also available. Table 1 and 2 describe commonly available diets and fasting methods. If adequately evaluated, such non-pharmacologic techniques' effect will help reduce the annual economic burden due to chronic neurological and other diseases.

In the United States, cancer is the second leading cause of death (1 in every 5), followed by heart disease. In 2020, about 1,603,844 new cancer cases were reported in the USA, and 602,347 patients died of cancer. (U.S. Department of Health and Human Services, 2023) It is critical to find new treatment modalities that could increase the efficacy of current treatment and decrease tumor cell growth. Tumor cells are not flexible with their primary energy source and require glucose. (Woolf et al., 2016) Tumor cells are characterized by higher glycolytic and pentose phosphate activity even

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in the presence of oxygen, and their high glucose uptake corresponds with poor prognosis in some tumors. (Ma et al., 2021; Voss et al., 2022)

The increasing prevalence of obesity has led to higher rates of morbidity and mortality related to various diseases such as diabetes, cancer, cardiovascular disorders, and cerebrovascular disorders. Consequently, healthcare costs have also risen significantly. To address this issue, effective obesity control measures are crucial to reduce or avoid the need for extensive medical expenses. (Li et al., 2022) The induction of ketosis through a low-carbohydrate diet led to lower blood glucose levels, resulting in reduced insulin secretion stimulation and a decreased stimulus for fat accumulation. Higher levels of ß-hydroxybutyrate were associated with a more significant loss of visceral adipose tissue, clinically significant as visceral adiposity is linked to metabolic syndrome and cardiovascular disease. (Perissiou et al., 2020)

The ketogenic diet (KD) and intermittent fasting (IF) are helpful nutritional interventions with minor reported side effects such as gastrointestinal symptoms, hyperuricemia, hypomagnesemia, renal calculi, and dyslipidemia, which are transient and easy to manage. (Verrotti et al., 2017) Recently, studies have given strong evidence of KD's therapeutic implications in weight loss, diabetes, cardiovascular disorder, polycystic ovarian syndrome, cancer, and chronic neurological disorders. (A Paoli et al., 2013) Also, AHA recommended that the intake of added sugar should vary from five teaspoons per day (or 80 calories) for an average adult woman with daily 1800 calories expenditure and nine teaspoons per day (or 144 calories) for an average adult man with daily 2200 calories expenditure. (Johnson et al., 2009) We aim to review the role of KD & IF in neurologic diseases, cancer, and obesity in this article.

Discussion

Dietary interventions greatly influence regulating metabolic disorders and associated comorbidities such as hypertension, diabetes, and hyperlipidemia. In the context of hypertension, the Dietary Approaches to Stop Hypertension (DASH) regimen has demonstrated efficacy in reducing blood pressure by as much as 11 mmHg among hypertensive individuals. (Challa et al., 2023) Atkin's diet, which is high in protein and fat and low in carbohydrates, has proven to improve satiety, glycemic control, and lipid profile. Noteworthy is its potential to mitigate seizure frequency in refractory epilepsy. However, symptoms like nausea, dizziness, constipation, and headache commonly occur with the Atkins diet. (Husain et al., 2004) Hence, alternatively, the Modified Atkins diet with carbohydrate restriction to 10g/day while encouraging high-fat foods shows better compliance and tolerability. (Kossoff & Dorward, 2008) Another diet known for reducing the risk of modern-day ailments like cardiovascular events and diabetes is the paleo diet. Rich in proteins and long-chain polyunsaturated fatty acids, this regimen's potential benefits are to be acknowledged, but with caution among osteoporosis patients due to its inherent calcium deficiency. (Kowalski & Bujko, 2012) The ketogenic diet, characterized by high fat, low carbohydrate, is proven to be prudent in weight loss, better metabolic profile, and emerging utility in various neurological disorders like epilepsy and dementia. Its potential to reduce the incidence of major adverse cardiovascular events by reversing type 2 diabetes, improving lipid profile, and weight loss is widely documented. However, compliance with this diet is impaired due to adverse effects like muscle cramps and changes in bowel habits. Furthermore, the potential for stimulating inflammation and, therefore, precipitating biological aging must be considered with the long-term use of a ketogenic diet. (Cicero et al., 2015, McKenzie et al., 2017). Table 1 and 2 describe commonly available diets and fasting methods.

Table 1. Types of diets and fasting methods.

Type of Diet	Description	Pros	Cons

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Atkins (Husain et al., 2004; Kossoff & Dorward, 2008; Mahdi, 2006; Reddy et al., 2002; Roberts et al., 2012)	Initially, carbohydrate intake must be restricted to 20g/day, with the allowance to consume as much protein and fat as desired.	· No limitation on the amount of protein and fat consumed · Weight loss and seizure reduction in epilepsy patients · Risk of dementia or mild cognitive impairment (high carbohydrate levels) · Modest improvement in day-time sleepiness for narcolepsy patients	· Side effects associated with ketosis: nausea, dizziness, constipation, headache, fatigue, smelly breath · Metabolic dehydration · Risk of hyperuricemia (leading to joint pain and gout), hypercalciuria (leading to kidney stones, hypocalcemia, and osteoporosis · Risk of permanent loss of kidney function in anyone with reduced kidney function
Modified Atkins Diet(Kossoff et al., 2006, 2011; Kossoff & Dorward, 2008; Sharma et al., 2013, 2015)	Carbohydrate intake is restricted to 10-15g/day for children and 15-20g/day for adolescents/adults with encouragement of high-fat foods (~65% of calories from fat sources)	· Less restrictive than the ketogenic diet · Decreased risk of growth impairment, kidney stones, dyslipidemia, gastroesophageal reflux · Seizure frequency reduction with about 45% of patients with epilepsy responding with greater than 50% seizure reduction	· Approximate 25-50 mg/dl increase in total cholesterol in both pediatric and adult studies · Increase in Blood Urea Nitrogen (BUN) levels
DASH (Challa et al., 2023)	Promotes consumption of vegetables and fruits, lean meat, and dairy products and the inclusion of micronutrients in the diet and advocates in the reduction of sodium in the diet to about 1500 mg/day	· Lowers blood pressure · Lowers risk of adverse cardiac events and stroke · Lowers blood glucose levels, triglycerides, LDL cholesterol, and insulin resistance · Improvements in control of type 2 diabetes · and reduction in the incidence of colorectal cancer (mainly in the white population)	· Not designed for weight loss
Paleo (Kowalski & Bujko,	Dietary plan is based on foods similar to foods that might have been eaten in	· Reduce the risk of cardiovascular disease, metabolic syndrome, type 2	· Low calcium intake. (risk for individuals at risk for osteoporosis)

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2012; Pitt, 2016)	the Paleolithic era, which dates to approximately 2.5 million to 10,000 years ago. Diet includes lean meats, fish, fruits, vegetables, nuts, and seeds.	diabetes, cancer, acne vulgaris, and myopia. · Favorable changes in risk factors, such as weight, waist circumference, glucose tolerance, insulin secretion, insulin sensitivity, and lipid profiles.	
Ketogenic Diet (Cicero et al., 2015; Grandl et al., 2018; Henderson et al., 2009; McKenzie et al., 2017)	High-fat, low carbohydrate diet (20-50gm/day) in which carbohydrates are nearly eliminated, thus enabling fatty acids to become the required obligatory source of cellular energy production by peripheral tissues and the brain.	· Increased Weight loss during the first 3-6 months compared with those who follow more balanced diets. · Reversal/control of Type 2 diabetes for primary and secondary prevention of cerebrovascular and cardiovascular disorders. · Reduction of serum triglycerides and improvement of lipid profiles. · Increase in the level of HDL cholesterol in obese patients. · Improvement of lipid disorders that are characteristic of atherogenic dyslipidemia. · Beneficial effects on neurological disorders include epilepsy and Alzheimer's disease.	· Muscle cramps, bad breath, changes in bowel habits, Keto-flu, and energy loss. · Long-term low-carbohydrate diets with increased fat consumption could stimulate inflammatory pathways and oxidative stress and promote biological aging, induction of hepatic insulin, micronutrient deficiencies, and cardiovascular safety.
Fasting (Devathasan & Koh, 1982; GENUTH, 1977; Greenfield et al., 1978; Kerndt et al., 1982; Lawlor et al., 1968)	24-hour-fast, Intermittent daily fasting 16:8 (Restriction: Intake) or 18:6, Skipping meals, One Meal A Day Fast, Water or egg fasting	· Control of Type 2 diabetes to mitigate cardiovascular and cerebrovascular disorders · Improvement in glucose tolerance. · Improvement of insulin sensitivity and glucose tolerance in people with diabetes immediately following a fast weight loss.	· Nausea and vomiting · Edema · Alopecia and motor neuropathy · Hyperuricemia and urate nephropathy · Irregular menses · Abnormal liver function tests and decreased bone density · Thiamine deficiency and Wernicke's encephalopathy · Mild metabolic acidosis

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		· Possible death (due to lactic acidosis, small bowel obstruction, renal failure, and cardiac arrhythmias)

Table 2. Various types of Fasting methods.

Type of Fasting	Description
24-hour-fast	Fast in which no food is consumed for 24 hours. Individuals can consume water, and in most cases, black coffee and/or green tea is allowed.
Intermittent daily fasting 16:8 (Anton et al., 2018)	Restricting food intake/fasting for 16 hours a day and consuming food for 8 hours a day
Skipping meals	Occasionally skipping meals such as breakfast, lunch, and/or dinner according to the individual's level of hunger or time restraints.
One Meal A Day Fast (OMAD)	Type of intermittent fasting is referred to as 23:1, in which an individual spends 23 hours fasting and leaves 1 hour a day to consume calories by eating and drinking.
Water fasting (Finnell et al., 2018)	Fasting is when a person does not eat and drink anything other than pure water; a "zero calorie diet."
Eggs fasting	Fast in which eggs are prepared without butter/oil and beverages such as water and zero-calorie beverages are permitted (use of artificial sugar is not recommended)

Mechanism of action and types of ketogenic diet

KD is a high-fat, low-carbohydrate diet (20-50gm/day) in which carbohydrates are nearly eliminated, thus enabling fatty acids to become the required obligatory source of cellular energy production by peripheral tissues and the brain. (A Paoli et al., 2013) Under normal dietary conditions, the brain utilizes glucose as an energy source; however, ketone bodies are the primary energy source during fasting. Under fasting conditions, fatty acids from the body fat are oxidized in the mitochondria to produce acetyl CoA, which is further used to synthesize ketone bodies such as ß-hydroxybutyrate and acetoacetate and used as an energy source. KDs mimic the metabolic state of fasting and maintain permanent ketosis. (Elia et al., 2018) Ketone bodies are implicated in symptomatic relief and disease-modifying activity in neurological disorders such as Alzheimer's and Parkinson's disease and maintain a neuroprotective role in stroke and traumatic brain injury. (Elia et al., 2018; Gasior et al., 2006) The effectiveness of a KD for neurological disorders stems from the efficiency of ketones over glucose as an energy source for brain cells and because ketone bodies have a higher inherent energy.(Augustin et al., 2018; Gasior et al., 2006)

Many subclasses of KD could be utilized. The classic KD is the most restrictive yet offers the highest ketogenic potential, with a ratio of grams of fat to the grams of carbohydrates and protein being 4:1 or 3:1 (other diet subclasses generally fall within 2:1 or 1:1). (Augustin et al., 2018; Verrotti et al., 2017) The medium-chain triglyceride (MCT) diet contains a high ketogenic potential because enterocytes readily absorb MCTs and rapidly converted to ketones by the body. (Augustin et al., 2018) Unlike the classic KD, in which 60-80% of dietary energy is provided by long-chain fats, in the MCT diet, only 45% of dietary energy is provided through medium-chain fats such as octanoic acid

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and decanoic acid. (Augustin et al., 2018) Therefore, the MCT diet allows a more extensive carbohydrate content; however, it is utilized less commonly than classic KD because of unpleasant gastrointestinal side effects. (Verrotti et al., 2017) Although the MCT diet is utilized less frequently, studies have shown that the MCT KD is used worldwide in treating drug-resistant epilepsy, especially in children. (Augustin et al., 2018) Lastly, the modified Atkins diet (MAD) and low glycemic index treatment (LGIT) are diets in which net daily carbohydrate consumption is limited to a specific amount per day and fat consumption is encouraged, ideally composed of 60-70% of total calories. (Roehl & Sewak, 2017) In the MAD, the net daily carbohydrate consumption is limited to 20 g for adolescents and adults and 15-20g for pediatric patients. In LGIT, the daily carbohydrate consumption is limited to 40-60g/day from foods that have a glycemic index <50 for both pediatric and adult patients. (Roehl & Sewak, 2017)

Neuroprotective Role of KD in Neurological Disorders:

The human studies showing the beneficial effects of KD are mentioned in Table 3.

Table 3. Human Studies Showing Beneficial Effects.

Clinical Conditions	Study, Country (Year)	Sample Size/Timeline	· Methods	· Findings
Epilepsy (Groesbeck et al., 2006)	Groesbeck et al., USA (2006)	28 patients (15 males, 13 females), currently aged 7 to 23 years	· Retrospective chart review of children treated with the KD for more than six years at the Johns Hopkins Hospital	· Twenty-four children experienced more than a 90% reduction in seizures over prolonged periods on KD, and 3 achieved complete freedom from seizures.
Epilepsy (Cervenka et al., 2017)	Cervenka et al., USA (2017)	Ten adults were treated with KD monotherapy for epilepsy (4 patients were naïve to anti-seizure drugs (ASDs), and six previously tried and stopped ASDs)	· Adults (age ≥ 18 years) evaluated in the Johns Hopkins Adult Epilepsy Diet Center (AEDC) from August 2010 to August 2016 were followed, and descriptive statistics were used to represent patient characteristics and outcomes.	· 50% of treatment-naïve participants were free from disabling seizures on the Modified Atkins Diet (MAD) monotherapy for > 1 year. · 67% (4 out of 6) of patients who previously tried ASDs became seizure-free on diet monotherapy. Two patients experienced >50% seizure reduction.
Epilepsy (Freeman et al., 1998)	Freeman et al., USA (1998)	150 consecutive children, ages 1 to 16 years, all of whom continued to have more than two	· Children were treated with the KD and followed for at least one year. · Seizure frequency was tabulated from patients' daily seizure calendars.	· The children (mean age, 5.3 years) averaged 410 seizures per month before the diet. · Three months after diet initiation, 83% remained on the diet,

		seizures per week despite therapy with at least two anticonvulsant medications	· Furthermore, seizure reduction was calculated as a percentage of baseline frequency.	and 34% had a >90% decrease in seizures. · At six months, 71% still remained on the diet, and 32% had a >90% decrease in seizures. · At one year, 55% remained on the diet, and 27% had a >90% decrease in seizure frequency.
Epilepsy (Hemingway et al., 2001)	Hemingway et al., USA (2001)	150 consecutive children entered prospectively into a study of the KDs efficacy and tolerability	· 3 to 6 years after diet initiation, all 150 families were sent a survey inquiring about their child's health status, seizure frequency, and anticonvulsant medications.	· Of the original 150-patient cohort, 20 (13%) were seizure-free, and 21 (14%) had a 90% -99% decrease in their seizures. · Twenty-nine were free of medications, and 28 were on only one; 15 remained on the diet.
Epilepsy (Marsh et al., 2006)	Marsh et al., USA (2006)	150 children with epilepsy, refractory to at least two medications, who initiated the KD between 1994 and 1996	· 3 to 6 years after diet initiation, all the families were contacted by telephone or questionnaire to assess their child's current seizure status, medications, and therapies.	· Almost half of the children who discontinued the diet during the first year had fewer seizures when assessed 3-6 years later. 22% of these had become seizure-free without surgery.
Stroke/ Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) (Steriade et al., 2014)	Steriade et al., USA (2014)	A 22-year-old woman with multiple episodes of generalized and focal status epilepticus and migratory cortical stroke-like lesions who underwent muscle biopsy for mitochondria	· Clinical, electrophysiologic, and radiologic data of the patient were analyzed.	· KD improves mitochondrial dysfunction in MELAS, which may promote better seizure control and less frequent stroke-like episodes.

		l genome sequencing		
Alzheimer's Diseases (Reger et al., 2004)	Reger et al., USA (2004)	20 subjects with AD or mild cognitive impairment	· Subjects consumed a drink containing emulsified MCTs or placebo and cognitive tests were administered, and levels of the ketone body β-hydroxybutyrate were observed through blood draws.	· MCT treatment facilitated performance on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) for APOE4(-) subjects but not for APOE4(+) subjects. · Higher ketone values were associated with greater improvement in paragraph recall with MCT treatment relative to placebo across all subjects.
Alzheimer's Diseases (Henderson et al., 2009)	Henderson et al., USA (2009)	152 subjects diagnosed with mild to moderate AD	· Daily administration of AC-1202, an oral ketogenic compound, was evaluated in subjects in a US-based, 90-day, randomized, double-blinded, placebo-controlled, parallel-group study. · Participants received one dose of the agent during the first seven days of the study, followed by two doses (20 g of MCT) administered at breakfast from day 8 to day 90.	· AC-1202 rapidly elevated serum ketone bodies in AD patients, resulting in significant differences in ADAS-Cog scores compared to the placebo. Effects were most notable in APOE4(-) dosage-compliant subjects.
Alzheimer's Diseases (Luchsinger et al., 2002)	Luchsinger et al., USA (2002)	80 Elderly individuals free of dementia were followed for four years.	· Daily intake of calories, carbohydrates, fats, and protein was recalled using a semiquantitative food frequency questionnaire between baseline and first follow-up visits.	· Individuals with the highest calorie intake compared to the lowest quartile had an increased risk of AD. (HR:1.5; 95% CI:1.0-2.2). · For individuals with the apolipoprotein E 4 allele, the hazard ratios of AD for the highest quartiles of calorie and

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				fat intake were 2.3 (95% CI, 1.1-4.7) and 2.3 (95% CI: 1.1-4.9), respectively, compared with the lowest quartiles.
Alzheimer's Diseases (Taylor et al., 2018)	Taylor et al., USA (2017)	7- Clinical Dementia Rating (CDR) 0.5, 4- CDR 1, and 4- CDR 2 participants (a total of 15 patients with AD) were enrolled in the KD Retention and Feasibility Trial	· 3-month, medium-chain triglyceride-supplemented KD followed by 1-month washout participants. Administered the Alzheimer's Disease Assessment Scale-cognitive subscale and Mini-Mental State Examination before the KD and following the intervention and washout.	· In achieving ketosis, the mean of the Alzheimer's Disease Assessment Scale cognitive subscale score improved significantly during the diet and reverted to baseline after the washout.
Alzheimer's Diseases (Krikorian et al., 2012)	Krikorian et al., USA (2012)	23 older adults with Mild Cognitive Impairment	· Patients were randomly assigned either a high carbohydrate or very low carbohydrate diet in a 6-week intervention.	· Improved verbal memory performance for the subjects on the low-carbohydrate diet was noted. The levels of ketone bodies were positively correlated with memory performance.
Migraine (Cherubino Di Lorenzo, Coppola, et al., 2019)	Di Lorenzo et al., Italy (2019)	18 migraine patients without aura before and after a 1-month of KD	· To prove if the KD-related cortical excitability changes are primarily due to cerebral cortex activity or are modulated by the brainstem. The study concurrently recorded the interictally nociceptive blink reflex (nBR) and the pain-related evoked potentials (PREP).	· Following 1-month on KD, the mean number of attacks and headache duration reduced significantly. KD significantly normalized the interictal PREP habituation, while the nBR habituation deficit did not change.
Migraine (C. Di Lorenzo et al., 2015)	Di Lorenzo et al., Italy (2017)	96 overweight female migraineurs patients	· Mean monthly attack frequency, number of days with headaches, and tablet intake were assessed before and 1, 2,	· Drastic improvement in attack frequency, days, and medication use during the one-month

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		(45: KD and 51: standard diet) for three months	3, and 6 months after diet initiation.	· (p<0.0001) followed by a worsening during the transitional diet and subsequent standard diet period. According to the authors, KD efficacy's underlying mechanisms could be related to its ability to enhance mitochondrial energy metabolism and counteract neural inflammation.
Migraine (Cherubino Di Lorenzo, Pinto, et al., 2019)	Di Lorenzo et al., Italy (2019)	Randomized Double-Blind, Cross-Over Trial of 35 overweight obese migraines.	· To determine the therapeutic effect of a very low-calorie diet in overweight episodic migraine patients during a weight-loss intervention in which subjects alternated randomly between a very low-calorie KD (VLCKD) and a very low-calorie non-KD(VLCnKD) each for one month. The primary outcome was reducing migraine days each month compared to a 1-month pre-diet baseline. Secondary outcome measures were a 50% responder rate for migraine days, reduction of monthly migraine attacks, abortive drug intake, and body mass index (BMI) change.	· VLCKD patients experienced fewer migraine days with respect to VLCnKD ($p < 0.0001$). · The 50% responder rate for migraine days was 74.28% (26/35 patients) during the VLCKD period but only 8.57% (3/35 patients) during VLCnKD. Migraine attacks decreased during VLCKD with respect to VLCnKD ($p < 0.00001$). · The two diets showed no differences in acute anti-migraine drug consumption ($p = 0.112$) and BMI ($p = 0.354$) between the two diets. · A VLCKD has a preventive effect in overweight episodic migraine patients that appears within one month, suggesting that ketogenesis may be a useful therapeutic strategy for migraines. VLCKD is effective for rapid, short-term improvement of migraines in

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				overweight patients, while VLCnKD is not. · Whether this dietary strategy should be applied to all overweight migraine patients and for how long remains to be determined in future studies.
Chronic Cluster Headache (Cherubino Di Lorenzo et al., 2018)	Di Lorenzo et al., Italy (2018)	18 drug-resistant chronic cluster headache (CCH) patients	· Patients underwent a 12-week KD (Modified Atkins Diet, MAD), and the clinical response was evaluated in terms of response (≥50% attack reduction).	· 3-month KD ameliorated clinical features of chronic cluster headache
Parkinson's Disease (VanItallie et al., 2005)	Vanitaille et al., USA (2005)	Seven patients with Parkinson's Disease	· Patients prepared a "hyperketogenic" diet at home for 28 days. Used the Unified Parkinson's Disease Rating Scale (UPDRS) to measure effects.	· A hyperketogenic diet at home and adherence for 28 days resulted in high ketogenic bodies, which improved the Unified Parkinson's Disease Rating Scale scores.
Parkinson's Disease (Phillips et al., 2018)	Phillips et al., USA (2018)	Forty-seven patients with Parkinson's disease (38 individuals completed the study).	· This study assessed the effect of a low-fat versus KD in patients. Diets were followed for eight weeks.	· Both diet groups showed significantly improved motor and non-motor symptoms; however, the ketogenic group showed greater improvements in non-motor symptoms.
Amyotrophic lateral sclerosis (ALS) (Veldink et al., 2006)	Veldink et al., Netherlands (2007)	A case-control study (132 patients and 220 healthy controls) between 2001–2002.	· Patients' dietary intake for the nutrients of fatty acids, cholesterol, glutamate, or antioxidants was assessed using a food-frequency questionnaire to evaluate their link with the risk of developing ALS.	· A high intake of PUFAs and vitamin E is associated with a 50–60% decreased risk of developing ALS, and these nutrients appear synergistically.
ALS (Okamoto et al., 2007)	Okamoto et al., Japan (2007)	The study comprised 153 patients and 306	· A self-administered food frequency questionnaire was used to estimate pre-	· The high intakes of carbohydrates and low intakes of fat and some kinds of fatty acids

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		gender- and age-matched controls randomly selected from the general population.	illness intakes of food groups and nutrients.	may, when combined, increase the risk of ALS.
Behavioral Disease (Jagust et al., 2005)	Jagust et al., USA (2005)	112 Latino individuals aged 60 years and above were selected from an ongoing larger cohort of 1789 individuals.	· Baseline anthropomorphic measures (WHR) and measurements of fasting blood glucose, cholesterol, insulin levels, and blood pressure were obtained. Baseline anthropomorphic measures (WHR) and measurements of fasting blood glucose, cholesterol, insulin levels, and blood pressure were obtained.	· The WHR and age were positively related to white matter hyperintensities (*p* = 0.02 and *p* = 0.001, respectively). A 1-SD increase in WHR was associated with a 0.2-SD decrease in hippocampal volume and a 27% increase in white matter hyperintensities. · A larger WHR may be related to neurodegenerative, vascular, or metabolic processes that affect brain structures underlying cognitive decline and dementia.

KD: Ketogenic Diet; IF: Intermittent Fasting

Epilepsy

Epilepsy is a severe neurological disease that results from aberrant, synchronous depolarization of neurons in the central nervous system and affects 1% of the United States population. (Gooch et al., 2017) Epilepsy is successfully controlled by one or more antiepileptic drugs (AEDs), but still, 35% of patients have refractory epilepsy. (Kwan et al., 2009; Picot et al., 2008) Since the 1920s, studies have found that KD is an effective treatment of epilepsy in both children and adults. (BARBORKA, 1928; Kverneland et al., 2015; Liu et al., 2018; Neal et al., 2008) A new variant of KD, particularly MAD and LGIT, provides a therapeutic mechanism, especially for individuals with medically intractable epilepsy, by reducing the onset of seizures, improving seizure frequency and severity, and improving these patients' quality of life (QOL) of these patients. (Agarwal et al., 2017; Elia et al., 2018; Koppel & Swerdlow, 2018; Nei et al., 2014; Roehl et al., 2019) A study by Agarwal et al. found that epileptic children who started KD at a young age show a more favorable response, >50% seizure reduction at 12-month follow-up. (Agarwal et al., 2017) However, utilizing the KD in adults and adolescents also shows response rates comparable to those in children.[47] Additionally, Seo et al. found that 80% of patients who failed to achieve seizure control relied on a lower ratio diet (3:1) and improved with a higher ratio diet (4:1). (Hee Seo et al., 2007) A randomized controlled trial by Neal et al. reported that

KD is significantly effective in treating drug-resistant epilepsy compared to no change in therapy. Considering the results of this study, we should consider KD with any AEDs in treating drug-resistant epilepsy. (Neal et al., 2008)

There are two mechanisms by which KD affects seizure control: a) Reducing the glucose concentration and increases fatty acid oxidation and ketones production, which offers a stabilized energy source to the brain in the form of ketones bodies and decreases the likelihood of disruptions in energy availability, which also decrease the possibility of seizures. b) Alternating neurotransmitter releases and uptake, ketone bodies, specifically acetoacetate and ß-hydroxybutyrate, decrease seizure activity by limiting γ-aminobutyric acid receptor-induced seizures. Also, KD with chronic ketosis may modify the tricarboxylic acid (TCA) cycle to limit reactive oxygen species (ROS) and boost energy production in the brain.(Elia et al., 2018) The specific actions of the KD in limiting ROS are due to their direct neuroinhibitory actions, such as: increasing GABA synthesis in the brain, inducing the expression of neuronal uncoupling proteins (UCPs), upregulating numerous energy metabolism genes, and inducing mitochondrial biogenesis.(Elia et al., 2018; Roehl & Sewak, 2017) The result of upregulating oxidative phosphorylation and limiting glucose also leads to neuron hyperpolarization by activating KATP channels, decreasing the onset of seizures. (Elia et al., 2018; Roehl & Sewak, 2017; Verrotti et al., 2017)

Stroke

Cerebral stroke, particularly ischemic stroke, is the leading cause of chronic disability and the second leading cause of dementia in the United States. (Sheyda Shaafi et al., 2014) A study by Shaafi et al. has reported the effect of KD on pathological conditions like oxidative stress, glutamate-mediated excitotoxicity, and apoptosis that occur in ischemic stroke.(Sheyda Shaafi et al., 2014) It has been shown that hyperglycemia aggravates ischemic stroke while ß-hydroxybutyrate provides a protective function.(Gasior et al., 2006; Sheida Shaafi et al., 2019; Sheyda Shaafi et al., 2014) In vitro study by Maalouf et al. showed that ketone bodies can protect from excitotoxicity and increase the survival time of the patients, also ketone bodies, through NADH oxidation regulation, reduce free radical-induced oxidative stress in neuronal cells and also reduce some apoptotic biomarkers.(Maalouf et al., 2007) Ketone bodies can protect neurons from glutamate excitotoxicity by allowing efficient glutamate removal and conversion to GABA, improving the neurons' free radical elimination ability, and reducing some apoptotic markers such as bax-mRNA and bax protein.(Sheida Shaafi et al., 2019)

Alzheimer's disease (AD)

AD is the leading cause of dementia, affecting as many as 2.4% of the US population.(Gooch et al., 2017) AD etiopathogenesis has been linked to oxidative stress, neuroinflammation, mitochondrial impairment, hypometabolism, and blood-brain barrier disruption. Studies have shown that amyloid ß accumulation is associated with toxic effects on the mitochondria, such as impaired energy homeostasis and impaired electron transport chain activity, which could consequently lead to cell death and cause synaptic damage seen in AD.(Augustin et al., 2018; Antonio Paoli et al., 2014) KD acts to induce anti-oxidant and anti-inflammatory activity in patients with AD. KD also stimulates nuclear factor erythroid-derived 2 (NF-E2)-related factor 2 (Nrf2), which induces endogenous detoxification and helps to alleviate oxidative stress associated with AD.(Pinto et al., 2018) Additionally, it decreases the production of Amyloid Precursor Protein (APP) and, therefore, the ß-amyloid peptide and also helps to activate peroxisome proliferator-activated receptor gamma (PPARγ), which plays a role in decreasing systemic inflammation. In particular, ß-hydroxybutyrate is one of the central ketone bodies detected in the blood following a KD and can cross the blood-brain barrier, lowering neuroinflammation by activating the hydroxyl-carboxylic acid receptor 2 (HCA2) and leading to memory improvement. Ketone bodies, ß-hydroxybutyrate in particular, were also found to be therapeutic in protecting against the production of toxic Aß plaques associated with AD.(Gasior et al., 2006; Pinto et al., 2018)

Traumatic brain injury (TBI)

TBI occurs when a traumatic event leads to rapid brain movement within the skull, resulting in brain damage. In the US, the annual incidence of TBI is 1.7 million, resulting in 12,000 deaths and 3.2 to 5.3 million persons with long-term disability. Elderly population ≥65 years accounts for 10% of these injuries, commonly due to falls and motor vehicle accidents. (Gooch et al., 2017) Limited understanding of the pathophysiology of TBI made it challenging to develop its clinical treatment. Primary brain injury in TBI can be prevented with medical care and secondary brain injury can be targeted to improve the outcomes. Secondary TBI leads to metabolic cellular dysfunction, cerebral edema, free radical damage, oxidative damage, ischemic injury, cerebral glucose metabolism disruption, and programmed cell apoptosis. The KD has a neuroprotective effect by inducing the state of ketosis and targeting the secondary brain injury phenomenon. (Prins et al., 2013) A review study by McDougall et al. found that KD is an effective treatment therapy for TBI where KD increases the ketone bodies in circulation and provides an alternative energy source to the brain. In addition, they are metabolically efficient and require less oxygen per ATP. KD inhibits cellular apoptosis and edema through this anti-inflammatory and anti-oxidative effect. (McDougall et al., 2018) It has also been shown that KD could play a role in significantly reducing cerebral edema post-traumatic brain injury (TBI), which is the leading cause of injury-related morbidity and mortality worldwide. (McDougall et al., 2018)

Migraine

Migraine is another disabling neurological disorder affecting 16.2% of the US population. (Gooch et al., 2017) Migraine primarily arises due to brain excitatory-inhibitory imbalance leading to episodic activation and sensitization of the trigeminovascular pain pathway, causing recurrent headaches and sensitivity to sensory stimuli. (Vecchia & Pietrobon, 2012) The diet is considered a critical factor in migraines because some foods can trigger the attack without scientific evidence. Many pieces of evidence suggest that KD may be an effective treatment in different stages of migraine, reinstating metabolism and excitability of the brain and protecting against neuroinflammation and redox mechanisms. (Barbanti et al., 2017) A study by Yudkoff et al. reported that KD could activate astrocyte metabolism, promoting glutamate conversion to glutamine, eventually converted to GABA, thus balancing the exciting and inhibitory neurotransmission in migraine and decreasing brain cortical excitability. (YUDKOFF et al., 2005)

Brain Tumor

Malignant brain tumors are devastating even after aggressive chemotherapy, radiation, and surgical resection. The average life expectancy of glioblastoma is 18 months after all treatments are available. Therefore, it is very critical to find new treatment modalities that increase the efficacy of current treatment and decrease the tumor cell growth, which can be achieved by using KD. The KD simulates fasting and leads to high production of acetyl CoA by fatty acid oxidation. When the amount of acetyl-CoA exceeds the capacity of the TCA Cycle to utilize it, the production of ketone bodies- βHB and ACA increases, which can be used as an energy source by the normal brain cells. However, tumor cells are not flexible with their primary energy source and require glucose. This metabolic dysregulation achieved by inducing KD may target the Warburg Effect in highly glycolytic tumors, such as malignant gliomas. (Woolf et al., 2016)

Amyotrophic Lateral Sclerosis (ALS)

ALS is a progressive neurodegenerative disorder in which metabolic dysfunction features upper and lower motor neuron demise, leading to muscle weakness, culminating in paralysis and, finally, death due to respiratory paralysis. (Tefera et al., 2017) Due to the multifactorial origin of ALS, no specific treatment is identified, and since there is mitochondrial involvement, KD can be an effective treatment modality. The metabolic dysfunction specifically, there is altered glucose uptake, and the C4-intermediate levels, such as ß-hydroxybutyrate of the TCA cycle, are decreased. (Tefera et al.,

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2017) These findings suggest that C4 ketones are an excellent source of alternative fuels that could help overcome problems associated with the reduced ability to use glucose as a fuel. Additionally, C4 ketones provide a variety of protective mechanisms, such as anti-oxidant and anti-inflammatory properties, that prove beneficial in ALS. (Tefera et al., 2017) In previous studies, the use of KD and MAD/LGIT reduced the loss of lower motor neurons in the ventral horn of the spinal cord. (Koppel & Swerdlow, 2018) It also showed that the administration of KD led to higher motor neuron survival and improved motor function. (Antonio Paoli et al., 2014)

Autism Spectrum Disorder (ASD)

ASD is one of the most prevalent developmental disorders today, with symptoms appearing during the first years of life and continuing throughout life. ASD has been linked to multiple metabolic disorders and shares traits with diseases related to epilepsy, such as Landau-Kleffner, Dravet, and Rett syndromes. Therefore, the positive effects of KD on epilepsy, when taken into account, has the potential to alleviate specific symptoms related to ASD, especially in females. (Napoli et al., 2014)

Role of Intermittent Fasting (IF) in Neuroprotection and Neurological Disorders:

Periods of deliberate fasting with restriction of solid food intake are being practiced worldwide. In the Western world, particularly the United States, the average calorie intake has risen along with the incidence of associated diseases such as cardiovascular disease, neurodegenerative disease, and obesity, with one-third of American adults and 20% of teenagers being obese. (Michalsen & Li, 2013) IF is a recurring method of eating in which individuals go extended periods (16-48 hours) with little or no energy intake and have intervening periods of regular food intake. (Mattson et al., 2017) This method decreases food intake and body weight and improves brain functions and structures. (Mattson et al., 2017; Vasconcelos et al., 2014) IF can be practiced with or without KD. In humans, caloric restriction has been shown to reduce markers of oxidative stress, inflammation, and cardiovascular disease risk, while in animal models, it has been shown to protect neurons against degeneration. (Manzanero et al., 2011) Evidence suggests that IF prevents oxidative damage by diminished production of mitochondrial reactive oxygen species (ROS), increased antioxidant defenses, and increased repair mechanisms for molecules damaged due to oxidation. (Manzanero et al., 2011; Michalsen & Li, 2013) Additionally, IF has been found to upregulate brain-derived neurotrophic factor (BDNF) in animal models by decreasing oxidative stress, increasing synaptic plasticity, neurogenesis, and cell survival. (Malinowski et al., 2019; Michalsen & Li, 2013) IF has also been associated with increasing heat shock protein 70 (HSP70), which offers neuroprotection via its anti-apoptotic role and downregulating Mammalian Target of Rapamycin (mTOR). This kinase allows for positive effects such as delayed aging, synaptic plasticity, and neurodegeneration due to autophagy's disinhibition. (Michalsen & Li, 2013) Similarly, the presence of inflammation can worsen the outcome of obesity, stroke, and neurodegenerative diseases, and studies have shown that IF can reduce the concentration of inflammatory markers such as interleukin 6 (IL-6) and C-reactive protein (CRP). (Malinowski et al., 2019; Michalsen & Li, 2013; Vasconcelos et al., 2014) There are primarily two critical proteins involved in the anti-inflammatory effect exerted by IF: mTOR and SIRT1. As previously mentioned, mTOR is a significant player in inflammation and is downregulated by IF. At the same time, SIRT1 is a deacetylase that is upregulated by IF and inhibits NFκB, a central transcription factor responsible for expressing many genes associated with inflammation. (Michalsen & Li, 2013)

Several IF regimens are hypothesized to impact health outcomes: complete alternate-day fasting, modified fasting regime, time-restricted feeding, and religious fasting. Alternate-day fasting involves days when no calories are consumed, followed by feeding days when foods and beverages are consumed as desired. In animal models, alternate-day fasting has been shown to reduce total plasma cholesterol and triglycerides and reduce liver steatosis and inflammation gene expression, and evidence in humans suggests that it can lead to modest weight loss and improvements in some metabolic parameters. On regularly scheduled fasting days, modified fasting regimens (also known

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as intermittent energy restriction) limit energy consumption to 20-25% of energy needs, resulting in weight loss with mixed effects on inflammatory markers. (Patterson & Sears, 2017) A time-restricted feeding regime involves a daily fasting interval of 12 to 21 hours. It has been associated with reduced body weight and inflammatory marker levels such as IL-6 and tumor necrosis factor α (TNF-α). Lastly, observational studies suggest that the religious fasting regimen results in transitory weight loss and mixed impacts on other biomarkers. (Patterson & Sears, 2017)

A health-promoting mechanism associated with IF includes the regulation of circadian rhythms. Because meal timing can significantly influence circadian rhythm, adopting an IF regime can exclude or reduce energy intake in the evening and nighttime, which could synchronize food ingestion with optimal postprandial hormone response times. (Mattson et al., 2017; Patterson & Sears, 2017) This could lead to improved energy metabolism mechanisms and body weight regulation. Studies have also shown that IF can slow the progression of neurodegenerative diseases such as Alzheimer's, Parkinson's, and stroke because it upregulates the expression of antioxidant enzymes (heme oxygenase 1), neurotrophic factors such as BDNF and FGF2, and protein chaperones (HSP70 and GRP78). (Mattson et al., 2017) Along with these factors, IF can suppress the inflammasome and reduce inflammation. (Mattson et al., 2017)

Role of KD & IF in Cancers

Prior studies suggest that the increased glycolysis seen in cancer cells appears to be a response to protect against increased hydroperoxide-mediated oxidative stress caused by altered mitochondrial metabolism. Therefore, strategies to utilize this mechanism in cancer cells might help amplify the effects of radiation and chemotherapy. (Ma et al., 2021) This suggested that diets like KD or a modified Atkins diet low in carbohydrates could selectively target the glycolytic tumors and thus complement the cancer therapy. For oncological purposes, KDs can be defined as a high-fat (usually ≥ 65% of energy intake), low-carbohydrate (≤ 50g per day) diet that ideally also provides an adequate protein supply (≈ 1.5 g/kg per day). Thus, fatty acids become the required obligatory source of cellular energy and target the Warburg Effect in highly glycolytic tumors. (Klement & Sweeney, 2022; Voss et al., 2022; Woolf et al., 2016)

The clinical trials describe KD and IF's role in brain cancer, non-metastasized rectal cancer, high-grade glioma (new and recurrent), head and neck squamous cell carcinoma, locally advanced and metastatic breast cancer, and ovarian and endometrial cancer. (Augustus et al., 2021; Cohen et al., 2020; Khodabakhshi et al., 2020, 2021; Klement, Koebrunner, et al., 2021; Klement, Weigel, et al., 2021; Klement & Sweeney, 2022; Ma et al., 2021; Porper et al., 2021; Voss et al., 2022) Results of these studies described KD as accompanying measure for cancer patients undergoing standard-of-care therapy that helps to improve the quality of life, survival with no severe side effects, and acceptable safety and tolerability in advanced cancer patients. Chemotherapy and radiotherapy with KD may have enhanced antitumor effects. (Table 4) Although the role of KD was described in depth, most RCT results were heterogeneous to provide quantitative measures of survival timeline, outcomes, and recovery. Thus, more prospective studies in humans are warranted to evaluate the potential therapeutic effectiveness and safety of KD.

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Table 4. Role of KD & IF in different types of cancer patients.

Type of Cancer	References / Studies included	Type of Diet	Total Patients & Intervention	Role of KD
Head and neck cancer (Klement & Sweeney, 2022)	Klement et al., Germany (2022)	KD (7) + SD (21)	28; with radiotherapy and chemotherapy	KD may partially counteract the detrimental effects of both radio and chemotherapy on body composition in HNC patients.
Brain Tumors (Voss et al., 2022)	Voss et al., Germany (2022)	KD + IF	20; with irradiation	The short diet schedule led to significant metabolic changes, with low glucose emerging as a marker of better prognosis.
Non-metastasized Rectal Cancer (Klement, Koebrunner, et al., 2021)	Klement et al., Germany (2021)	KD (18) + SD (23)	41; during radiotherapy	This study demonstrated a trend for KDs contributing synergistically to pathological tumor response.
High-grade glioma- new (6), recurrent (7) (Porper et al., 2021)	Porper et al., Israel (2021)	KD + KD & Metformin	13; with radiotherapy	Higher serum ketone levels were associated with both dietary intake and metformin use.
Head and Neck Squamous Cell Carcinoma (Ma et al., 2021)	Ma et al., USA (2021)	KD	12; 8 patients with concurrent radiation and platinum-chemotherapy	This study demonstrated difficulty with diet compliance when combined with standard-of-care radiation therapy and cisplatin chemotherapy.
Breast Cancer (Klement, Weigel, et al., 2021)	Klement et al., Germany (2021)	KD (29) + SD (30)	59; during radiotherapy	It supports that consuming a KD during radiotherapy is safe for women with breast cancer and has the potential to improve quality of life and metabolic health.

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Locally advanced and metastatic breast cancer (Khodabakhshi et al., 2021)	Khodabakhshi et al., Iran (2020)	KD + SD	80; with chemotherapy	KD in breast cancer patients might exert beneficial effects by decreasing TNF-α and insulin and increasing IL-10. KD may result in a better response through reductions in tumor size and downstaging in patients with locally advanced disease.
Locally advanced and metastatic breast cancer (Khodabakhshi et al., 2020)	Khodabakhshi et al., Iran (2019)	KD + SD	60; with chemotherapy	Results suggested that a combination of chemotherapy and KDs could improve the biochemical parameters, body composition, and overall survival with no substantial side effects in breast cancer patients.
Ovarian and Endometrial Cancer (Cohen et al., 2020)	Cohen et al., USA (2020)	KD + SD	57; with usual care	The findings suggest that KD may be a safe and achievable component of treatment for some cancer patients.
Stage II and III Cancer Patients (Augustus et al., 2021)	Augustus et al., West Indies (2020)	KD	NA	KD was suitable for Stage II and III cancer patients in improving their quality of life and nutritional, functional, and psychosocial statuses.

KD: Ketogenic Diet; IF: Intermittent Fasting; SD-Standard Diet

Role of KD in Obesity:

There is strong supportive evidence in favor of KD being a very effective weight loss therapy, with some contrasting theories regarding its mechanism of action in weight loss. The most likely explanation for KD's effectiveness in weight loss is its appetite-suppressing action of ketosis. In addition, reduced appetite due to the higher satiety effect of proteins and modification in levels of hormones like ghrelin and leptin, which influence appetite, increased lipolysis, reduced respiratory quotient, increased metabolic rate to consume fats, and increased gluconeogenesis and thermic effect of protein are several factors that can aid in weight loss on KD. (A Paoli et al., 2013) Ghrelin, a neuropeptide hormone that stimulates feeding behavior, is released in response to dieting. Sumithran

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et al. studied 39 patients where the expected release of ghrelin and increased appetite were alleviated when the subjects were in ketosis. (Sumithran et al., 2013)

Very Low-Calorie KDs (VLCKDs) may promote quicker hepatic fat mobilization than other compartments, and this effect is likely due to the ketogenic state rather than calorie restriction alone, making it a potential treatment option for conditions like Non-alcoholic Fatty Liver Disease. (Cunha et al., 2020) Moreover, patients with obesity and mild renal failure over three months noted that 27.7% of patients with mild renal impairment experienced a return to normal glomerular filtrate after the VLCKD dietary intervention. (Bruci et al., 2020) Choi et al. evaluated ketogenic nutrition drinks with different ketogenic ratios and concluded that the production of ketone bodies was induced and maintained through the consumption of a ketogenic nutrition drink with a more moderate ketogenic ratio (1.7:1) than the typical ratio of 4:1. (Choi et al., 2018) Overweight or obese adult females with abnormal glucose control factors may benefit from implementing a low-calorie KD (LCKD) combined with weight loss interventions and insulin resistance avoidance. However, they can present unique challenges as research subjects due to hormonal influences; further investigations are necessary to assess the long-term safety and effectiveness of the proposed dietary strategy. (Michalczyk et al., 2020) Additionally, long-term adherence to KD was found to be challenging, so periodic KDs could be beneficial for newly diagnosed overweight or obese patients with type 2 diabetes mellitus by helping manage their blood glucose and lipid levels, as well as promoting weight loss. (Li et al., 2022) (Table 5)

Table 5. - Role of KD in Obesity.

	Study, Country (Year)	**Sample Size/Timeline**	**Methods**	**Findings**
Obesity, Visceral fat, and Liver fat Accumulation (Cunha et al., 2020)	Cunha et al., Brazil, (2020)	39 patients (20 VLCKD, 19 LC) for two months	· Prospective study to determine the efficacy of VLCKD compared to LCD in reducing Visceral and Liver fat accumulation in patients with obesity.	· At two months, the VLCKD group had a relative weight reduction of 9.59 2.87%, while the LC group had a relative weight loss of 1.87 2.4% (p 0.001). The average VAT reductions were 32 cm2 for the VLCKD group and 12 cm2 for the LC group (p 0.05). The VLCKD group experienced reductions in the liver fat fraction that were noticeably more severe than those in the LC group (4.77 vs. 0.79%; p<0.005).
Obesity and Mild kidney failure (Bruci et al., 2020)	Bruci et al., Rome, (2020)	92 individuals (38 – mild renal disease, 54-	· A prospective observational study where participants underwent VLCKD	· Notable decrease in fat mass, average weight loss close to 20% of initial weight, improvement

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		no renal disease), for three months	for three months. Anthropometric parameters, bioelectrical impedance, and biochemistry were gathered before and after dietary intervention.	in metabolic markers, and GFR returned to normal at 27.7% after intervention in the group with mild renal disease.
Severe obesity and NAFLD (D'Abbondanza et al., 2021)	Abbondanza et al., Italy (2020)	100 subjects- 72 severely obese women, 28 severely obese men (BMI ≥ 40, BMI ≥ 35 with obesity-related comorbidities, age between 18 and 65 years, followed for 25 days	· All subjects were evaluated at enrolment and 25 days after following VLCKD. Statistical analysis determined the difference in primary endpoints (Excess of body weight loss (EBWL), reduction in GGT). Secondary endpoints (variations of obesity grade according to EOSS, degree of liver steatosis).	· Significant weight loss, fat mass, and degree of steatosis were observed in all groups. Males experienced significantly larger EBWL, and greater GGT reduction, and higher waist circumference, insulin resistance, and HbA1c reduction than females.
Obesity or overweight with newly diagnosed Type 2 DM (Li et al., 2022)	Li et al., China (2022)	60 patients with overweight or obesity newly diagnosed with Type 2 DM, 30 on KD, 30 on standard diabetes diet for twelve weeks.	· Variables such as uric acid, insulin, blood lipids, body weight, and blood glucose were measured before and after intervention.	· A significant decrease in rates of weight, BMI, waist circumference, TG, Cholesterol, LDL, HDL, FBG, Fasting insulin, and HbA1C was noted in the KD group compared to the control group.
Obesity and Overweight (Di Rosa et al., 2022)	Rosa et al., Italy (2022)	268 obese patients randomly assigned to MLCKD or VLCKD,	· Population stratified according to gender, BMI, and age. · Follow-up visits were done monthly until 5%	· Both groups lost 5 %body weight but required different periods (VLCKD – 1 month, MD group- 3 months)

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		maximum of 3 months, or lose 5 % body weight	body weight loss, anthropometric parameters, and body composition were obtained at the end of the study.	· Higher waist circumference and fat mass percentage reduction in the MD group compared to the VLCKD group.
Obesity- Cardiorespiratory fitness, Body composition, Cardiometabolic risk factors (Perissiou et al., 2020)	Perissiou et al., Australia (2020)	64 obese men and women were randomly assigned to experiment al (structured exercise +low carbohydrat e meals) and control (structured exercise+ standard dietary advice) for eight weeks	· Blocked randomization stratification applied by gender, Anthropometric parameters, blood biomarkers, and cardiorespiratory fitness obtained at the study's beginning and end, data was statistically analyzed between the experimental and control groups.	· A more significant increase in cardiorespiratory fitness (measured by delta V O2 peak – mean diff -3.4), a greater reduction in fat mass index, lean muscle mass, fasting blood glucose, triglycerides, and CRP was noted in the experimental group than the control group. Reaching a ketogenic status was associated with a significant decrease in total body fat, visceral adipose tissue, fat mass index, and lean muscle mass.
Hyperinsulinemic overweight / Obese (Michalczyk et al., 2020)	Michalczyk et al., 2020, Poland	100 females who reported to the clinic were randomly assigned to LCKD and control group followed for 12 weeks, 4 in LCKD, 5 in control resigned	· A tailor-made hypocaloric diet was prescribed for each subject, where daily caloric consumption was 20 % less than total daily energy expenditure. Blood biochemical analysis, body mass measurement, and circumference measurement were measured at the beginning and end of the study.	· Compared to baseline, there was a decrease in glucose, insulin, HbA1c, TG, insulin resistance, body mass, waist circumference, hip circumference, thigh circumference, increase in HDL- C among the LCKD group after intervention. These changes are not observed in the control group. The LCKD group had lower glucose, insulin, HbA1c, insulin resistance, body mass, waist

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				circumference, hip and thigh circumference, and an increase in HDL-C compared to the control group after the intervention.
Obesity (Choi et al., 2018)	Choi et al., 2018, South Korea	46 subjects between 19-49 years, BMI>25, intervention for two weeks	· Subjects were randomly assigned to 3 groups with equal gender distribution – 1. Ketogenic nutrition drink (fat: carb – 4:1), 2. Modified ketogenic nutrition drink (1.7:1), 3. Balanced nutrition drink. Measurements like anthropometric measurements, body composition analysis, blood lipid profile, and ketone bodies were performed before the intervention, during (after one week), and after (2 weeks) intervention. Changes in physical activity and body symptoms were surveyed through questionnaires.	· Saturated fat intake was high among KD 4:1 compared to KD 1.7:1. All groups showed a decrease in body water and minerals from 0 weeks to 1 week, with no significant change from 1 to 2 weeks. Protein and skeletal muscle mass decreased significantly in KD 4:1, BD groups. All groups showed decreased BMI, Body fat mass, and weight. A decrease in total cholesterol and LDL cholesterol was seen in KD 1.7:1 and BD groups, with no significant changes in KD 4:1 group. Ketone bodies significantly increased in KD 4:1 and KD 1.7:1 from 0 to 1 week, with no change from 1 to 2 weeks. Nausea, decreased appetite significantly increased from 0 to 1 week in KD 4:1, KD 1.7:1. Constipation significantly increased in KD 4:1 group.

Very Low-Calorie Ketogenic Diets (VLCKDs); Low-Calorie Diets (LC diets)

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Role of IF in Obesity

IF, which could be done for one day (IF1) or two days straight (IF2) per week, is frequently utilized to achieve the best possible body weight loss results. In a randomized control trial, IF2-P resulted in significantly more significant body weight and waist circumference reductions than IF1-P. It also showed a strong tendency for more substantial reductions in fat mass, glucose, hunger levels, and hormone responses. (Arciero et al., 2022) From pre- to post-intervention, the time-restricted eating (TRE)/ time-restricted feeding (TRF) group experienced considerably more significant losses of total body mass and fat mass than the standard eating group. In conclusion, the use of TRE and concurrent exercise training as a short-term dietary therapy for persons who are overweight or obese to reduce fat mass and increase lean mass. (Kotarsky et al., 2021) Overweight older men and women (aged 65–74) with visceral fat were evaluated to see how well a six-week TRE intervention reduced body weight, fat loss, and visceral fat. While both men and women significantly lost body weight after the six-week TRE intervention, waist circumference, and visceral fat mass were significantly decreased in men. (Domaszewski et al., 2023) Combining IF with concurrent exercise programs was proven to be more effective results of weight loss, improved biomarkers compared to diet alone therapy. (Maaloul et al., 2023; Salis et al., 2022) Compared to regular calorie restriction, patients on the IF 5:2 program (30% of energy requirements on fast days and 70% on non-fast days) were more successful in losing weight. (Kang et al., 2022; Witjaksono et al., 2022) (Table 6)

Table 6. Role of IF in Obesity.

	Study, Country, (Year)	**Sample size/ Timeline**	**Methods**	**Findings**
IF + protein pacing (Arciero et al., 2022)	Arciero et al., USA (2022)	42 participants, 21 to intervention (10 assigned to IF1-P, 10 to IF2-P), five weeks of intervention.	· Randomized controlled trial where 42 were eligible, 20 IF-P matched for weight, BMI, randomly assigned to either a) IF diet for one day/week (36 hours), protein pacing diet for remaining six days/week, or b) Intermittent diet for two consecutive days (60 hours) and protein pacing for remaining five days/week. All lab testing procedures were performed at baseline control (week 0), and in week 5, ITT analysis was conducted.	· Dietary energy and macronutrient intake decreased; specifically, total energy intake decreased significantly (40%) during weight loss, with no difference in groups. IF2-P group had greater body weight and waist circumference than IF1-P; Fat-free mass increased by 2%. No significant hormone changes in both groups from baseline were noted. Both groups had significant reductions in BP, fasting total cholesterol, LDL-C, and triglycerides from baseline, with

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				no differences between groups. Significant reduction in desire to eat and quantity of food to eat, the tendency of hunger ratings lower in IF2P compared to IF1-P ·
Intermittent vs. continuous energy restriction (Headland et al., 2019)	Headland et al., Australia (2018)	332 overweight and obese adults between 18-72 years, randomly assigned to 1 of 3 groups 1) Continuous energy restriction, 2) week on week off restriction, 3) 5:2 restriction for a total of 12 months.	· Randomized, parallel trial design to compare three different dietary patterns 146 completed study, all three groups visited the clinic every three months, a total of eight visits. Participants were grouped based on gender, BMI, and age, randomized 1:1 to intervention groups, · Only 56%of participants finished the trial. Primary outcome was weight loss. Secondary outcomes were changes in body composition, weight loss, and glucose.	· ITT analysis showed a significant effect of interventions on weight loss at 12 months, although there were no differences between the three groups. Fat and lean mass decreased significantly over time, with no differences between the dietary groups. HDL increased, and triglycerides decreased by a similar degree in all groups.
IF and concurrent exercise (Kotarsky et al., 2021)	Kotarsky et al., USA, (2021)	Twenty-one participants with a BMI of 25-34.9 were randomly assigned to normal eating (NE) or time-restricted eating (TRE),	· Randomized control trials. Body composition, muscle performance, energy intake, macronutrient intake, physical activity, and physiological variables were assessed between both groups.	· Mild energy restriction was observed in TRE and NE. Loss of total body mass was more significant for the TRE group compared to both the NE group and pre-intervention. Lean mass increased during intervention for both TRE and

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		resistance training, and aerobic exercise standardized for both groups for eight weeks.		NE with no differences.
IF on body weight, composition, vital signs in low-income women with obesity (de Oliveira Maranhão Pureza et al., 2021)	Puerza et al., Brazil, (2021)	58 women were randomized to hypo energetic diet and time-restricted diet for 12 months.31 lost to follow up.	· Randomized controlled trial. · Body fat and waist circumference were measured at baseline and after 4,6, and 12 months of intervention. Systolic and diastolic blood pressure, heart rate, and axillary temperature were measured at baseline and 12 months of intervention.	· ITT analysis showed no significant changes in body weight after 12 months. An increase in axillary temperature, a reduction in percentage body fat, and waist circumference were observed in the interventional group compared to the control group.
IF – overweight older men and women(Domaszewski et al., 2023)	Domaszewski et al., Poland, (2023)	116 healthy, non-smoking participants assigned to time-restricted eating (TRE) or educational control participants for six weeks	· TRE group were advised not to consume calories for 16 hrs/day, control group to continue the previous diet. Changes in body weight and composition were compared.	· TRE group had a decrease in body weight in both men and women. A significant reduction in visceral fat mass and waist circumference was observed in men. No changes in visceral fat or waist circumference were seen in women.
IF vs. IF with concurrent training (Maaloul et al., 2023)	Maaloul et al., Tunisia (2023)	Twenty obese men regularly performing Ramadan diurnal intermittent fasting (RDIF) were randomized	· Randomized controlled trial. Body composition, blood glucose, lipid profile, and inflammation were assessed before and after the 4-week RDIF.	· Both groups had decreased weight, fat mass, fat percentage, and waist circumference and improved blood glucose, lipid profile, and inflammation. Fat-

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		into two groups: a) RDIF with concurrent training (RDIF-CT) and b) RDIF without training (RDIF-NCT) for four weeks.		free mass decreased significantly in RDIF-NCT compared to the RDIF-CT group. RDIF-CT group showed more remarkable improvement in body composition (weight, fat mass, fat percentage, waist circumference) and a more significant decrease in lipid biomarkers, inflammation, and liver damage compared to RDIF - NCT group pre - post-intervention.
IF, weight loss (Salis et al., 2022)	Salis et al., India, (2022)	32 overweight /obese adults were assigned consecutively to an IF plan and followed up for three months	· Demographic, anthropometric, and dietary assessments were done pre and post-intervention. Qualitative interviews were done at the end of the study to record the participants' overall well-being, experience, and sustainability of IF	· Significant reductions in mean body weight, waist circumference, BMI, daily calories, carbohydrate intake, and increased protein intake were noted. Participants reported positive experiences of practicing IF, such as improved fitness, sleep cycle, and adoption of healthy eating habits.
IF 5:2 plus program (Kang et al., 2022)	Kang et al., China (2022)	131 participants in three groups 1) IF group (n= 42) 2) Daily calorie restriction group (CR)(n=1) 3) Daily calorie	· In this retrospective cohort study, participants were divided into two groups: 1) IF 5:2 plus groups – 30% of energy requirement on fast days, 70% on rest, 2) Daily calories restriction group: 70% of daily energy requirement given. Clinical data such as	· A mean weight loss of 7.8 after 12 weeks was noted. Weight change from baseline is higher in IF and HP groups compared to the CR group. BMI, fat mass, and total mass of all three groups were significantly decreased at 12

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		restriction with high protein meal replacement group (HP) (n=48); 12-week weight loss data analyzed	age, sex, weight, and body composition at 0 and 12 weeks, data on adverse events were also collected	weeks compared to baseline. No serious adverse events were reported in the three groups.
IF 5:2 (Witjaksono et al., 2022)	Witjaksono et al, Indonesia (2022)	50 participants, 25 allocated to the fasting group, and 25 to the control group for eight weeks	· Non-blinded 1:1 two-arm randomized control trial, the fasting group fasted twice a week (5:2) while the control group did not fast. Interviews were conducted before, during, and after an intervention to gather data on education, income, knowledge, physical activity, and food intake history. Per protocol, analyses were done.	· Significant differences in total calories, carbohydrate, protein, and fat intake between intervention and control groups after intervention. No significant difference in fat mass, skeletal muscle, and visceral fat rating before and after the study in intervention and control groups. Fat-free mass before and after showed a significant difference.

Evidence-based Recommendations:

KD is a low-carbohydrate diet (20-50gm/day) that seems effective and safe to consume under guidance. (“Summaries for Patients. Effectiveness and Safety of Low-Carbohydrate Diets.,” 2004) Gradually reducing carbohydrates in the diet before introducing KD can improve tolerance. Transition to KD can be sudden or over a week, and it should be done under the physician's supervision. Patients should be advised about common side effects like constipation, headache, bad breath, muscle cramps, diarrhea, general weakness, and rash.(“Summaries for Patients. Effectiveness and Safety of Low-Carbohydrate Diets.,” 2004) Other unfavorable changes are gradual increments in total cholesterol and LDL-C levels but favorable changes in triglyceride and probably HDL-C values. (Nordmann et al., 2006) Before starting KD, it is essential to get a baseline lipid profile, hemogram, thyroid profile, and renal function tests (Guisado Rosa, 2015), and monitor lipid profile, thyroid profile, and renal function during the diet, as few patients may show worsening parameters. So, regular watch on lipid profile becomes necessary, though no strict timeline is studied. A tool kit to measure ketone bodies is available in the market to measure to evaluate the optimal level. Long-term use of a KD may progressively reduce bone-mineral content (Bergqvist et al., 2008; Nordmann et al., 2006) and result in other nutritional deficiencies, so regular check-ups or replacement options should be evaluated.

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Consulting a physician if concurrent disorders like type 1 diabetes mellitus, renal impairment, and thyroid are present is strongly advised. KD can be short-term or long-term, but withdrawal must be gradual after achieving the goal, and adding 10 gm of carbohydrates per day for the first week is recommended. Healthy carbohydrates and more protein sources on the plate are suggested; adding more fiber (Ispaghula, aka Psyllium) to avoid constipation is advised. While absolute contraindications for KD include disorders of fat metabolism, porphyria, and pyruvate carboxylase deficiency, relative contraindications for KD are propofol concurrent use, parent or caregiver noncompliance, and inability to maintain adequate nutrition.(Kossoff et al., 2018) Although there is no current recommendation for the amount of ketosis to be achieved for beneficial effects in cancer, very low carbohydrate KD seems to be beneficial in patients starting KD in cancer. (Klement & Kämmerer, 2011) Research on KD for epilepsy shows that blood β-hydroxybutyrate greater than 4 mmol/L is necessary to deliver promising clinical outcomes, which is superior to the urine ketone dipstick test. (Gilbert et al., 2000)

It is important to note that the concentration of ketone bodies has to be more than 4 mmol/L to be utilized by the brain as an energy source. (Antonio Paoli et al., 2015) The ideal to measure ketosis is after dinner or early morning. (Urbain & Bertz, 2016)

Conclusion

The mechanism underlying the beneficial effects of KD and IF needs to be well studied. However, the neuroprotective effect is more likely to have mitigated excitotoxicity, oxidative stress, and apoptosis events and enhanced mitochondrial energy metabolism to counteract neural inflammation. Through all these mechanisms, both are reported as effective therapeutic interventions in treating various common neurological disorders with different clinical presentations. These findings suggest that the KD holds promise as a potential adjunctive therapy in various neurological disorders, offering new avenues for treatment and neuroprotection. While KD is commonly used for weight loss, there is limited literature about its effectiveness and safety in neurological disorders in humans. IF has shown potential in slowing the progression of neurodegenerative diseases such as Alzheimer's and Parkinson's by promoting antioxidant defense and suppressing inflammation. Different IF regimens offer flexibility in implementation and may have varying effects on biomarkers. Thus, further prospective human studies are warranted to evaluate more details about the potential therapeutic mechanism, effectiveness, and safety of both KD and IF.

KD and IF show promise in cancer therapy by targeting altered cancer cell metabolism. Some of the most robust reports of keto's possible benefits have come from glioblastoma, a very aggressive brain cancer. However, it does not work on other kinds of brain cancer. There has been minimal evidence that a high-fat, low-carb diet may help suppress solid prostate, breast, stomach, and liver cancers. Nevertheless, researchers have not ruled out the possibility that a KD may worsen cancer by promoting tumor growth; also, very low-fat diets have been shown to lower the chances that certain types of breast cancer may come back.

Additionally, KD may enhance the effects of standard therapies like chemotherapy and radiotherapy. More research is needed to understand cancer treatment's therapeutic potential and safety fully. These dietary interventions offer exciting possibilities as complementary measures for cancer management.

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