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Review

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

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Abstract

Ketogenic diet (KD) and intermittent fasting (IF) are non-pharmacologic nutritional therapies with modest side effects such gastrointestinal discomfort, dyslipidemia, and hypomagnesemia for various medical conditions. KD and IF may help with weight loss, diabetes, cardiovascular disease, polycystic ovarian syndrome, cancer, and chronic neurological illnesses. We studied KD and IF's impact on cancer, obesity, and neurodegenerative illnesses. We advised evidence-based KD and IF safety. KD is hard to maintain despite benefits. Thus, occasional KD adoption may help newly diagnosed overweight or obese type 2 diabetics lose weight and control blood glucose and lipids. KD is a high-fat, low-carbohydrate diet with 4:1 or 3:1 fat to carbohydrates and protein, thus peripheral tissues and the brain need fatty acids for energy. Most fasting energy comes from ketones. KD has been reliably used to treat refractory epilepsy since the 1920s. KD prevents epilepsy, stroke, severe brain injury, Alzheimer's, and other neurological illnesses. KD has been used to treat obesity since the 1960s. Combining chemotherapy and radiation with KD may increase tumor cell sensitivity. Thus, KD can be used to treat obesity, cancer, and chronic neurological disease without medicine or side effects. As an adjuvant therapy, KD may offer new neuroprotection and neuroscience treatments. Antioxidant defense and inflammation reduction may alleviate Alzheimer's and Parkinson's risk. By targeting cancer cell metabolism, KD and IF may be used to treat cancer. Radiation and chemotherapy may be intensified when used in conjunction with KD. In aggressive brain cancer glioblastoma, KD is most promising. Ketosis suppresses hunger, aiding weight loss in overweight or obese patients. Among type 2 diabetes patients, it helps to manage blood glucose and cholesterol, but long-term adherence is difficult. If paired with exercise, IF may be more effective than calorie restriction for weight loss. Further prospective human trials are needed to assess KD and IF's therapeutic efficacy and safety.

Keywords: Ketogenic diet; Intermittent fasting; Neurological disorders; Traumatic brain injury; Alzheimer's disease; Behavioral disease; Cancer; Obesity

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Introduction

In the USA, 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 [1]. In the breakdown of both direct (medical) and indirect (non-medical) costs, it was found that conditions such as Alzheimer's disease (AD), dementia, chronic low back pain,

stroke, traumatic brain injury (TBI), migraine headaches, epilepsy, multiple sclerosis, and Parkinson's disease had the highest annual expenditure [1]. 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 USA with no change in physical activity [2]. 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. Tables 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 USA, cancer is the second leading cause of death (one in every five), 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 [3]. 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 [4]. Tumor cells are characterized by higher glycolytic and pentose phosphate activity even in the presence of oxygen, and their high glucose uptake corresponds with poor prognosis in some tumors [5, 6].

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 [7]. 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 β-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 [8].

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 [9]. 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 [10]. Also, the American Heart Association (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 1,800 calories expenditure, to nine teaspoons per day (or 144 calories) for an average adult man with daily 2,200 calories expenditure [2]. We aimed to review the role of KD and IF in neurologic diseases, cancer, and obesity in this article.

Methods

Endpoints

The primary aim of our study was to evaluate the effectiveness of KD in various chronic conditions like neurological disorders, cancer, and obesity.

Search strategy and selection criteria

We performed a systematic review of previously published studies using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines from last 10 years. We used PubMed to find observational or interventional studies.

We used keywords (ketogenic diet (Title/Abstract) OR one meal a day (Title/Abstract) OR (Atkin diet (Title/Abstract) OR DASH (Title/Abstract) OR Paleo (Title/Abstract) OR (intermittent fasting (Title/Abstract) OR modified Atkins diet (Title/Abstract) OR OMAD (Title/Abstract)) to identify various types of diet and used keywords (obesity (Title/Abstract) OR cancer (Title/Abstract) OR epilepsy (Title/Abstract) OR chronic conditions (Title/Abstract) OR stroke (Title/Abstract) OR Alzheimer's disease (Title/Abstract) OR migraine (Title/Abstract) OR neurological disorders (Title/Abstract) OR neuroprotection (Title/Abstract) OR tumor (Title/Abstract) OR cardiorespiratory fitness (Title/Abstract) OR hyperinsulinemic state (Title/Abstract) OR diabetes (Title/Abstract)) to identify various chronic conditions.

Any literature other than case reports, review articles, and animal studies were excluded. Non-English literature, non-full text, and non-human studies were excluded. Flow diagram of the study selection process is described in Figure 1.

Study selection

All studies were identified using the search strategy described above and screened independently for their eligibility, and any disagreement was resolved through discussion with senior authors. Studies describing observational and interventional studies were considered for full-text evaluation.

Data extraction

A data extraction form on an Excel sheet was used to extract data from the included studies for the assessment of literature synthesis. Extracted information included: study setting (study name, year of publication), type of the diet, mechanism of action for the diet, effectiveness of KD and IF, chronic conditions, and cancers. Two authors extracted the data independently and the differences identified were resolved through discussion with the senior author.

Ethical approval

Though this article does not contain any studies with direct involvement of human participants or animals performed by any of the authors, all procedures performed in studies involving human participants were in accordance with the ethical stand-

Table 1. Types of Diets and Fasting Methods

Type of diet	Description	*Pros*	*Cons*
Atkins [15-19]	Initially, carbohydrate intake must be restricted to 20 g/day, with the allowance to consume as much protein and fat as desired.	No limitation on the amount of protein and fat consumed	Side effects associated with ketosis: nausea, dizziness, constipation, headache, fatigue, smelly breath
		Weight loss and seizure reduction in epilepsy patients	Metabolic dehydration
		Risk of dementia or mild cognitive impairment (high carbohydrate levels)	Risk of hyperuricemia (leading to joint pain and gout), hypercalciuria (leading to kidney stones, hypocalcemia, and osteoporosis
		Modest improvement in day-time sleepiness for narcolepsy patients	Risk of permanent loss of kidney function in anyone with reduced kidney function
Modified Atkins diet [16, 28, 29, 30]	Carbohydrate intake is restricted to 10 - 15 g/day for children and 15 - 20 g/day for adolescents/ adults with encouragement of high-fat foods (about 65% of calories from fat sources)	Less restrictive than the ketogenic diet	Approximate 25 - 50 mg/dL increase in total cholesterol in both pediatric and adult studies
		Decreased risk of growth impairment, kidney stones, dyslipidemia, gastroesophageal reflux	Increase in blood urea nitrogen (BUN) levels
		Seizure frequency reduction with about 45% of patients with epilepsy responding with greater than 50% seizure reduction	
DASH [20]	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 1,500 mg/day	Lowers blood pressure	Not designed for weight loss
		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)	
Paleo [21, 22]	Dietary plan is based on foods similar to foods that might have been eaten in 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.	Reduce the risk of cardiovascular disease, metabolic syndrome, type 2 diabetes, cancer, acne vulgaris, and myopia.	Low calcium intake (risk for individuals at risk for osteoporosis)
		Favorable changes in risk factors, such as weight, waist circumference, glucose tolerance, insulin secretion, insulin sensitivity, and lipid profiles.	

Table 1. Types of Diets and Fasting Methods - *(continued)*

Type of diet	Description	*Pros*	*Cons*
Ketogenic diet [11-14]	High-fat, low carbohydrate diet (20 - 50 g/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.	Muscle cramps, bad breath, changes in bowel habits, keto-flu, and energy loss
		Reversal/control of type 2 diabetes for primary and secondary prevention of cerebrovascular and cardiovascular disorders.	Long-term low-carbohydrate diets with increased fat consumption could stimulate inflammatory pathways, oxidative stress and promote biological aging, induction of hepatic insulin, micronutrient deficiencies and cardiovascular safety.
		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.	
Fasting [23-27]	24-h-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	Nausea and vomiting
		Improvement in glucose tolerance	Edema
		Improvement of insulin sensitivity and glucose tolerance in people with diabetes immediately following a fast weight loss	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
			Possible death (due to lactic acidosis, small bowel obstruction, renal failure, and cardiac arrhythmias)

LDL: low-density lipoprotein; HDL: high-density lipoprotein.

Table 2. Various Types of Fasting Methods

Type of fasting	Description
24-h fast	Fast in which no food is consumed for 24 h. Individuals can consume water, and in most cases, black coffee and/or green tea is allowed.
Intermittent daily fasting 16:8 [31]	Restricting food intake/fasting for 16 h a day and consuming food for 8 h 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 (OMAD) fast	Type of intermittent fasting is referred to as 23:1, in which an individual spends 23 h fasting and leaves 1 h a day to consume calories by eating and drinking.
Water fasting [32]	Fasting in which 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)

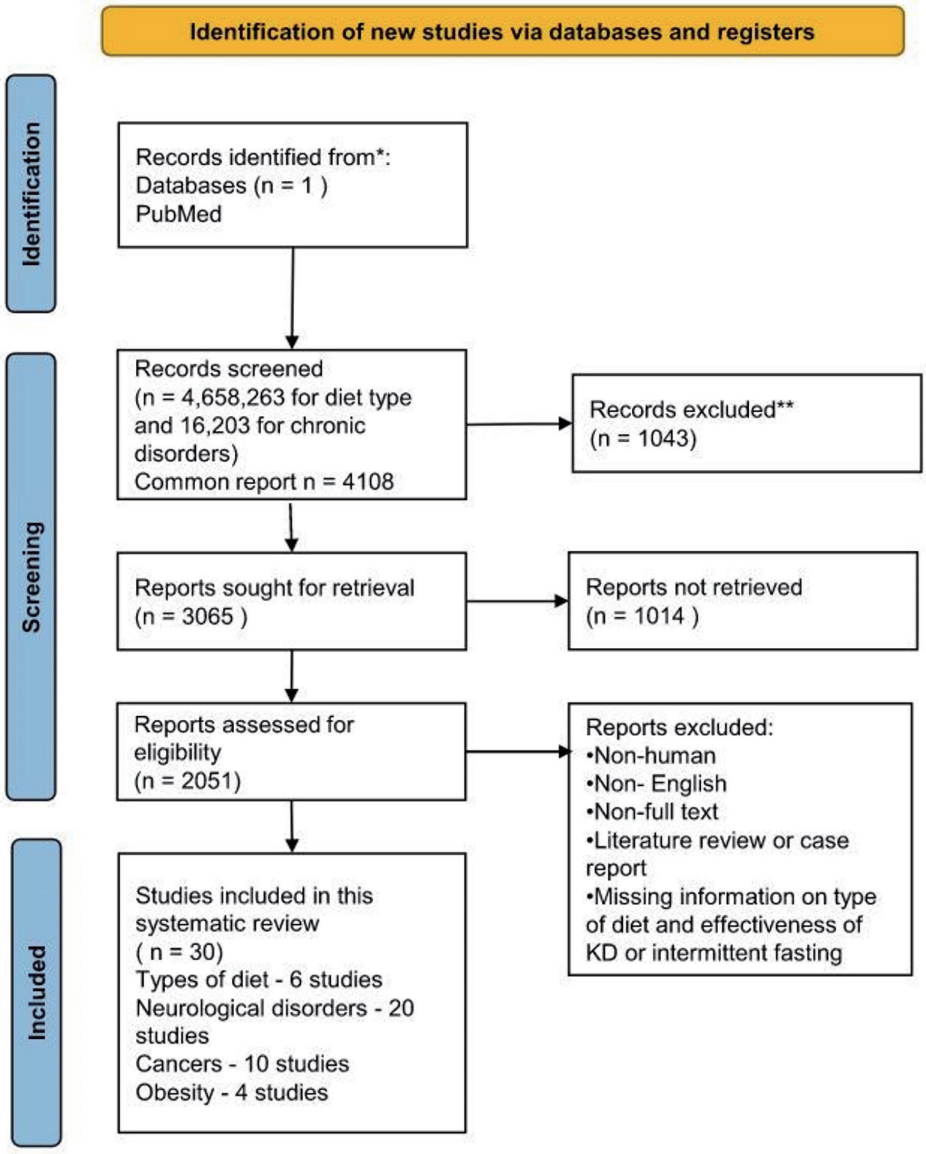

Figure 1. Flow diagram of the study selection process. KD: ketogenic diet.

ards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Out of 4,658,263 articles on various types of diet and 16,203 articles on chronic disorders and cancers, 4,108 articles had information on the effectiveness of any diet to control or improve chronic disorders, of which 2,051 studies have specific information on the effectiveness of the KD and IF in various disorders. After applying inclusion and exclusion criteria, we found six studies describing types of diet, 20 studies on neurological disorders, 10 on cancers, and four on obesity.

Types of diet

The KD is a high-fat, low-carbohydrate dietary regimen characterized by limited carbohydrate intake (20 - 50 g/day), leading to fatty acids becoming the primary source of cellular energy production, particularly in the brain [11-14]. Its potential benefits include weight loss, reversal/control of type 2 diabetes, improved lipid profiles, and favorable effects on neurological disorders such as epilepsy and Alzheimer's disease. However, it is associated with various adverse effects such as muscle cramps, bad breath, changes in bowel habits, and ketoflu [11-14]. Modified versions of the KD, such as the Atkins and modified Atkins diets (MADs), offer less restrictive alternatives, showing similar benefits in seizure reduction for epilepsy patients with fewer adverse effects [15-19]. Other diets like the DASH and Paleo diets focus on different nutritional approaches, with the former aimed at reducing blood pressure and cardiovascular risks, and the latter emphasizing whole foods similar to those consumed in the Paleolithic era [20-22]. IF, another dietary strategy, offers benefits in controlling type 2 diabetes and improving glucose tolerance, but it comes with potential risks such as nausea, vomiting, and metabolic acidosis [23-27]. Table 1 [11-30] and Table 2 [31, 32] describe commonly available diets and fasting methods [11, 14].

Role of KD in neuroprotection and neurological disorders

The provided articles cover a wide range of clinical conditions and the effects of KD on these conditions [13, 33-51]. For epilepsy, various studies indicate promising outcomes, with significant reductions in seizure frequency observed in both children and adults following KD treatment [33-37]. Additionally, KD shows potential benefits in conditions such as stroke and mitochondrial disorders like mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), where it may improve mitochondrial dysfunction and lead to better seizure control [38]. In Alzheimer's disease, studies suggest that KD and medium-chain triglyceride (MCT) supplementation could improve cognitive function, especially in individuals without the apolipoprotein E 4 (APOE4) allele [13, 39]. Moreover, KD demonstrates efficacy in migraine treatment, with reductions in attack frequency and duration observed in several studies [43, 45, 46]. Other neurological conditions such as Parkinson's disease and amyotrophic lateral sclerosis (ALS) also show potential for improvement with KD intervention [47-50]. Furthermore, the KD may have implications in metabolic disorders, as evidenced by its association with decreased risk factors for cognitive decline and dementia in elderly individuals [51]. Overall, the research underscores the diverse therapeutic potential of the KD across various neurological and metabolic conditions. The human studies showing the beneficial effects of KD are mentioned in Table 3 [13, 33-51].

Role of KD in cancer management

The articles reviewed encompass various cancer types and investigate the role of KD and other dietary interventions in cancer treatment [6, 52, 53-59]. Results suggest that KD may counteract the detrimental effects of radiotherapy and chemotherapy on body composition in head and neck cancer patients and contribute synergistically to pathological tumor response in non-metastasized rectal cancer patients [52, 53]. Additionally, KD and IF show promising metabolic changes and potential prognostic benefits in brain tumor patients [6]. Moreover, KD during radiotherapy appears safe and may improve quality of life (QOL) and metabolic health in breast cancer patients [55], while a combination of chemotherapy and KDs may improve biochemical parameters and overall survival in locally advanced breast cancer patients without substantial side effects [56, 57]. These findings suggest that KD may play a role in cancer treatment as a safe and achievable component, potentially improving treatment outcomes and QOL for some cancer patients. (Table 4) [5, , 6, 52, 54,55].

Role of KD and IF in obesity

The KD demonstrates effectiveness in weight loss therapy through various mechanisms such as appetite suppression, increased satiety effect of proteins, modification in hormone levels, increased lipolysis, and metabolic rate. Studies indicate that very low-calorie KDs (VLCKDs) can promote hepatic fat mobilization and potentially reverse mild renal impairment. However, long-term adherence to KD can be challenging, prompting the consideration of periodic KDs for managing conditions like type 2 diabetes mellitus. On the other hand, IF has emerged as an effective strategy for weight loss, with variations like IF1 and IF2 showing significant reductions in body weight, fat mass, and glucose levels. Time-restricted eating (TRE) combined with exercise training has also shown promise in reducing fat mass and visceral fat, particularly in overweight and older populations. Combining IF with exercise programs yields more favorable outcomes compared to diet alone therapy. Overall, both KD and IF offer potential benefits for obesity management, with further research needed to explore their long-term safety and effectiveness. (Table 5) [10, 60-68].

Table 3. Studies Showing Neuroprotective Effects of KD

Clinical conditions	Study author, country (year)	Sample size/timeline	Methods	Findings
Epilepsy [33]	Groesbeck et al, USA (2006)		Retrospective chart review of children treated with the KD for more than 6 years at the Johns Hopkins Hospital	24 children experienced more than a 90% reduction in seizures over prolonged periods on KD, and 3 achieved complete freedom from seizures.
Epilepsy [34]	Cervenka et al, USA (2017)	Ten adults were treated with KD monotherapy for epilepsy (4 patients were naive to 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-naive participants were free from disabling seizures on the 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 [36]	Freeman et al, USA (1998)	150 consecutive children, ages 1 to 16 years, all of whom continued to have more than two seizures per week despite therapy with at least two anticonvulsant medications	Children were treated with the KD and followed for at least 1 year. Seizure frequency was tabulated from patients' daily seizure calendars. Furthermore, seizure reduction was calculated as a percentage of baseline frequency.	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, and 34% had a > 90% decrease in seizures. At 6 months, 71% still remained on the diet, and 32% had a > 90% decrease in seizures. At 1 year, 55% remained on the diet and 27% had a > 90% decrease in seizure frequency.
Epilepsy [37]	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. 29 were free of medications, and 28 were on only one; 15 remained on the diet.
Epilepsy [35]	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/MELAS [38]	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 mitochondrial genome sequencing	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.

Table 3. Studies Showing Neuroprotective Effects of KD - *(continued)*

Clinical conditions	Study author, country (year)	Sample size/timeline	Methods	Findings
AD [39]	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 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.
AD [13]	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 7 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.
AD [40]	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 APOE4 allele, the HR of AD for the highest quartiles of calorie and 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.
AD [41]	Taylor et al, USA (2017)	7: 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 ADAS-Cog subscale and Mini-Mental State Examination before the KD and following the intervention and washout.	In achieving ketosis, the mean of the ADAS-Cog subscale score improved significantly during the diet and reverted to baseline after the washout.
AD [42]	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.

Table 3. Studies Showing Neuroprotective Effects of KD - *(continued)*

Clinical conditions	Study author, country (year)	Sample size/timeline	Methods	Findings
Migraine [43]	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 [46]	Di Lorenzo et al, Italy (2014)	96 overweight female migraineurs patients (45: KD and 51: standard diet) for 3 months	Mean monthly attack frequency, number of days with headaches, and tablet intake were assessed before and 1, 2, 3, and 6 months after diet initiation.	Drastic improvement in attack frequency, days, and medication use during the 1-month ($P < 0.0001$), 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 [45]	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 VLCKD and a VLCnKD each for 1 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. VLCKD has a preventive effect in overweight episodic migraine patients that appears within 1 month, suggesting that ketogenesis may be a useful therapeutic strategy for migraines. VLCKD is effective for rapid, short-term improvement of migraines in overweight patients, while VLCnKD is not.

Table 3. Studies Showing Neuroprotective Effects of KD - *(continued)*

Clinical conditions	Study author, country (year)	Sample size/timeline	Methods	Findings
				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 [44]	Di Lorenzo et al, Italy (2018)	18 drug-resistant chronic cluster headache (CCH) patients	Patients underwent a 12-week KD (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 [47]	Vanitaille et al, USA (2005)	7 patients with Parkinson's Disease	Patients prepared a "hyperketogenic" diet at home for 28 days. Used the UPDRS to measure effects.	A hyperketogenic diet at home and adherence for 28 days resulted in high ketogenic bodies, which improved the UPDRS scores.
Parkinson's disease [48]	Phillips et al, USA (2018)	47 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 8 weeks.	Both diet groups showed significantly improved motor and non-motor symptoms; however, the ketogenic group showed greater improvements in non-motor symptoms.
ALS [49]	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 [50]	Okamoto et al, Japan (2009)	The study comprised 153 patients and 306 gender- and age-matched controls randomly selected from the general population.	A self-administered food frequency questionnaire was used to estimate pre-illness intakes of food groups and nutrients.	The high intakes of carbohydrates and low intakes of fat and some kinds of fatty acids may, when combined, increase the risk of ALS.
Behavioral Disease [51]	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.

MELAS: mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; ALS: amyotrophic lateral sclerosis; ASD: anti-seizure drug; CDR: Clinical Dementia Rating; MAD: modified Atkins diet; KD: ketogenic diet; IF: intermittent fasting; UPDRS: Unified Parkinson's Disease Rating Scale; VLCKD: very low-calorie KD; VLCnKD: very low-calorie non-KD; AD: Alzheimer's disease; HR: hazard ratio; CI: confidence interval; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive; MCT: medium-chain triglyceride; APOE4: apolipoprotein E4; PUFA: polyunsaturated fatty acid; SD: standard deviation; WHR: waist-to-hip ratio.

Table 4. Role of KD and IF in Different Types of Cancer Patients

Type of cancer (n)	References/studies included	Type of diet	Total patients/intervention	Role of KD
Head and neck cancer [52]	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 head and neck cancer patients.
Brain tumors [6]	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 [55]	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, recurrent [54]	Porper et al, Israel (2021)	KD + KD and metformin	13/with radiotherapy	Higher serum ketone levels were associated with both dietary intake and metformin use.
Head and neck squamous cell carcinoma [5]	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 [55]	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.
Locally advanced and metastatic breast cancer [56]	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 [57]	Khodabakhshi et al, Iran (2021)	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 [58]	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 [59]	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; IL: interleukin; TNF: tumor necrosis factor; NA: not available.

Table 5. Ketogenic Diet and Intermittent Fasting in Obesity

Aspect	Findings
Weight loss mechanisms [10, 60-62]	KD induces weight loss through appetite suppression, increased satiety effect of proteins, modification in hormone levels, increased lipolysis, and metabolic rate. IF results in significant reductions in body weight, fat mass, and glucose levels.
Very low-calorie KDs (VLCKDs) [63, 64]	VLCKDs promote hepatic fat mobilization and may reverse mild renal impairment.
Challenges and considerations [65-68]	Long-term adherence to KD can be challenging, prompting the consideration of periodic KDs for managing conditions like type 2 diabetes mellitus. IF variations like IF1 and IF2 demonstrate significant reductions in body weight and fat mass. Combining IF with exercise programs yields more favorable outcomes compared to diet alone therapy.
Time-restricted eating (TRE) [61, 62]	TRE combined with exercise training has shown promise in reducing fat mass and visceral fat, particularly in overweight and older populations.

KD: ketogenic diet; IF: intermittent fasting.

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 mm Hg among hypertensive individuals [20]. Atkin's diet, which is high in protein and fat and low in carbohydrates, has been 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 [15]. Hence, alternatively, the MAD with carbohydrate restriction to 10 g/day while encouraging high-fat foods shows better compliance and tolerability [28]. 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 [21]. 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.

Mechanism of action and types of ketogenic diet

KD is a high-fat, low-carbohydrate diet (20 - 50 g/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 [10]. 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 β-hydroxybutyrate and acetoacetate and used as an energy source. KDs mimic the metabolic state of fasting and maintain permanent ketosis [69]. 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 TBI [69, 70]. 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 [70, 71].

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 combined grams of carbohydrates and protein being 4:1 or 3:1 (other diet subclasses generally fall within 2:1 or 1:1) [9, 71]. The MCT diet contains a high ketogenic potential because MCTs are readily absorbed by enterocytes and rapidly converted to ketones by the body [71]. 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 and decanoic acid [71]. 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 [9]. 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 [71]. Lastly, the 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 [72]. 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 - 60 g/day from foods that have a glycemic index < 50 for both pediatric and adult patients [72].

Neuroprotective role of KD in neurological disorders

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 US population [1]. Epilepsy is successfully controlled by one or more antiepileptic drugs (AEDs), but still, 35% of patients have refractory epilepsy [73, 74]. Since the 1920s, studies have found that KD is an effective treatment of epilepsy in both children and adults [75-78]. 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' QOL of these patients [69, 72, 79-81]. A study by Agarwal et al found that epileptic children who started KD at a young age show a more favorable response, with > 50% seizure reduction at 12-month follow-up [79]. However, utilizing the KD in adults and adolescents also shows response rates comparable to those in children. 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) [82]. A randomized controlled trial (RCT) 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 [78].

There are two mechanisms by which KD affects seizure control: 1) 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 decrease the likelihood of disruptions in energy

availability, which also decrease the possibility of seizures; 2) Alternating neurotransmitter releases and uptake, ketone bodies, specifically acetoacetate and β-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 [69]. The specific actions of the KD in limiting ROS are due to their direct neuroinhibitory actions, such as: increasing gamma aminobutyric acid (GABA) synthesis in the brain, inducing the expression of neuronal uncoupling proteins (UCPs), upregulating numerous energy metabolism genes, and inducing mitochondrial biogenesis [69, 72]. The result of upregulating oxidative phosphorylation and limiting glucose also leads to neuron hyperpolarization by activating KATP channels, decreasing the onset of seizures [9, 69, 72].

Stroke

Cerebral stroke, particularly ischemic stroke, is the leading cause of chronic disability and the second leading cause of dementia in the USA [83]. A study by Shaafi et al reported the effect of KD on pathological conditions like oxidative stress, glutamate-mediated excitotoxicity, and apoptosis that occur in ischemic stroke [83]. It has been shown that hyperglycemia aggravates ischemic stroke while β-hydroxybutyrate provides a protective function [70, 83, 84]. *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 [85]. 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 [84].

AD

AD is the leading cause of dementia, affecting as many as 2.4% of the US population [1]. AD etiopathogenesis has been linked to oxidative stress, neuroinflammation, mitochondrial impairment, hypometabolism, and blood-brain barrier disruption. Studies have shown that amyloid β 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 [10, 71]. KD acts to induce antioxidant 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 [86]. Additionally, it decreases the production of amyloid precursor protein (APP), and therefore the β-amyloid peptide, and also helps to activate peroxisome proliferator-activated receptor gamma (PPARγ), which plays a role in decreasing systemic inflammation. In particular, β-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, β-hydroxybutyrate in particular, were also found to be therapeutic in protecting against the production of toxic Aβ plaques associated with AD [70, 86].

TBI

TBI occurs when a traumatic event leads to rapid brain movement within the skull, resulting in brain damage. In the USA, 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. The elderly population ≥ 65 years accounts for 10% of these injuries, commonly due to falls and motor vehicle accidents [1]. 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. KD has a neuroprotective effect by inducing the state of ketosis and targeting the secondary brain injury phenomenon [87]. 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 adenosine triphosphate (ATP). KD inhibits cellular apoptosis and edema through this anti-inflammatory and antioxidative effect [88]. It has also been shown that KD could play a role in significantly reducing cerebral edema post-TBI, which is the leading cause of injury-related morbidity and mortality worldwide [88].

Migraine

Migraine is another disabling neurological disorder affecting 16.2% of the US population [1]. 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 [89]. 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 [90]. A study by Yudkoff et al reported that KD could activate astrocytes metabolism, promoting glutamate conversion to glutamine, eventually converted to GABA, thus balancing the exciting and inhibitory neurotransmission in migraine and decreasing brain cortical excitability [91].

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 (ACA) 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 [4].

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 [92]. 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 is characterized by altered glucose uptake, and the decreased levels of C4-intermediate, such as β-hydroxybutyrate of the TCA cycle [92]. 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 antioxidant and anti-inflammatory properties, which have been proved to be beneficial in ALS [92]. 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 [80]. It also showed that the administration of KD led to higher motor neuron survival and improved motor function [10].

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 [93].

Role of 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 USA, 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 [94]. IF is a recurring method of eating in which individuals go extended periods (16 - 48 h) with little or no energy intake and have intervening periods of regular food intake [95]. This method decreases food intake and body weight and improves brain functions and structures [95, 96]. 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 [97]. Evidence suggests that IF prevents oxidative damage by diminished production of mitochondrial ROS, increased antioxidant defenses, and increased repair mechanisms for molecules damaged due to oxidation [94, 97]. 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 [94, 98]. 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 [94]. 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) [94, 96, 98]. 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 [94].

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 as intermittent energy restriction) limit energy consumption to 20-25% of energy needs, resulting in weight loss with mixed effects on inflammatory markers [99]. A time-restricted feeding regime involves a daily fasting interval of 12 to 21 h. 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 [99].

A health-promoting mechanism associated with IF includes the regulation of circadian rhythms. Because meal tim-

ing 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 [95, 99]. 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 fibroblast growth factor 2 (FGF2), and protein chaperones (HSP70 and GRP78) [95]. Along with these factors, IF can suppress the inflammasome and reduce inflammation [95].

Role of KD and 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 [5]. This led to the suggestion that diets like KD or a MAD 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 (≤ 50 g and day) diet that ideally also provides an adequate protein supply (about 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 [6, 52, 4].

The clinical trials described 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 [5, 6, 52, 54, 55, 57-59]. Results of these studies described KD as an accompanying measure for cancer patients undergoing standard-of-care therapy that helps improve the QOL, 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.

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 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 [10]. Ghrelin, a neuropeptide hormone that stimulates feeding behavior, is released in response to dieting. Sumithran et al studied 39 patients where the expected release of ghrelin and increased appetite were alleviated when the subjects were in ketosis [100].

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 [63]. Moreover, patients with obesity and mild renal failure over 3 months noted that 27.7% of patients with mild renal impairment experienced a return to normal glomerular filtrate after the VLCKD dietary intervention [64]. 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 [101]. 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 [102]. 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 (Table 6) [8, 63-65, 101-104].

Role of IF in obesity

IF, which could be done for 1 day (IF1) or 2 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 significant reductions in fat mass, glucose, hunger levels, and hormone responses [60]. 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 [61]. Overweight older men and women (aged 65 - 74) with visceral fat were evaluated to see how well a 6-week TRE intervention reduced body weight, fat loss, and visceral fat. While both men and women significantly lost body weight after the 6-week TRE intervention, waist circumference and visceral fat mass were significantly decreased in men [62]. Combining IF with concurrent exercise programs was proven to be more effective results of weight loss, improved biomarkers compared to diet alone therapy [67, 105].

Table 6. Role of KD in Obesity

Disease	Study, country (year)	Sample size/timeline	Methods	Findings
Obesity, visceral fat, and liver fat accumulation [63]	Cunha et al, Brazil (2020)	39 patients (20 VLCKD, 19 LC) for 2 months	Prospective study to determine the efficacy of VLCKD compared to LCD in reducing visceral and liver fat accumulation in patients with obesity.	At 2 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 cm^2 for the VLCKD group and 12 cm^2 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 [64]	Bruci et al, Rome (2020)	92 individuals (38 mild renal disease, 54 no renal disease), for 3 months	A prospective observational study where participants underwent VLCKD for 3 months. Anthropometric parameters, bioelectrical impedance, and biochemistry were gathered before and after dietary intervention.	Notable decrease in fat mass, average weight loss close to 20% of initial weight, improvement in metabolic markers, and GFR returned to normal at 27.7% after intervention in the group with mild renal disease.
Severe obesity and NAFLD [103]	D'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 [65]	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 12 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 [104]	Rosa et al, Italy (2022)	268 obese patients randomly assigned to MD or VLCKD, maximum of 3 months, or lose 5 % body weight	Population stratified according to gender, BMI, and age.	Both groups lost 5 %body weight but required different periods (VLCKD: 1 month, MD group: 3 months)
			Follow-up visits were done monthly until 5% 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.

Table 6. Role of KD in Obesity - *(continued)*

Disease	Study, country (year)	Sample size/timeline	Methods	Findings
Obesity-cardiorespiratory fitness, body composition, cardiometabolic risk factors [8]	Perissiou et al, Australia (2020)	64 obese men and women were randomly assigned to experimental (structured exercise + low carbohydrate meals) and control (structured exercise + standard dietary advice) for 8 weeks	Blocked randomization stratification applied by gender, anthropometric parameters, blood biomarkers, and cardiorespiratory fitness obtained at the study's beginning and end, data were statistically analyzed between the experimental and control groups.	A more significant increase in cardiorespiratory fitness (measured by delta VO_2 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, VAT, fat mass index, and lean muscle mass.
Hyperinsulinemic overweight/obese [102]	Michalczyk et al, Poland (2020)	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 circumference, hip and thigh circumference, and an increase in HDL-C compared to the control group after the intervention.
Obesity [101]	Choi et al, Korea (2018)	46 subjects between 19 - 49 years, BMI > 25, intervention for 2 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 1 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-C 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.

KD: ketogenic diet; VLCKDs: very low-calorie ketogenic diets; LCKD: low-calorie ketogenic diet; LC: low-calorie; BMI: body mass index; NAFLD: non-alcoholic fatty liver disease; DM: diabetes mellitus; VAT: visceral adipose tissue; LDL: low-density lipoprotein; HDL: high-density lipoprotein; GGT: gamma-glutamyl transferase; EOSS: Edmonton Obesity Staging System; MD: Mediterranean diet; CRP: C-reactive protein; FBG: fasting blood glucose; GFR: glomerular filtration rate; HbA1c: hemoglobin A1c; TG: triglycerides.

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 (Table 7) [60-62, 66, 67, 68, 105-107].

Evidence-based recommendations

KD is a low-carbohydrate diet (20 - 50 g/day) that seems effective and safe to consume under guidance [108]. 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 [108]. Other unfavorable changes are gradual increments in total cholesterol and low-density lipoprotein (LDL) cholesterol (LDL-C) levels but favorable changes in triglyceride and probably high-density lipoprotein (HDL) cholesterol (HDL-C) values [109]. Before starting KD, it is essential to get a baseline lipid profile, hemogram, thyroid profile, and renal function tests [110] 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 [109, 111] and result in other nutritional deficiencies, so regular check-ups or replacement options should be evaluated.

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 g 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, i.e., 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 [28]. 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 [34]. Research on KD for epilepsy shows that blood β-hydroxybutyrate greater than 4 mmol/L necessary to deliver promising clinical outcomes, which is superior to the urine ketone dipstick test [112].

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 [113], and the ideal to measure ketosis is after dinner or early morning [114].

Conclusions

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 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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Conflict of Interest

Authors declare no conflict of interest.

Informed Consent

The data used in this study is identified from previously published studies so informed consent is not required.

Table 7. Role of IF in Obesity

	Study, country, (year)	Sample size/timeline	Methods	Findings
IF + protein pacing (P) [60]	Arciero et al, USA (2022)	42 participants, 21 to intervention (10 assigned to IF1-P, 10 to IF2-P), 5 weeks of intervention.	RCT where 42 were eligible, 20 IF-P matched for weight, BMI, randomly assigned to either 1) IF diet for 1 day/week (36 h), protein pacing diet for remaining 6 days/week; or 2) Intermittent diet for 2 consecutive days (60 h) and protein pacing for remaining 5 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 no differences between groups. Significant reduction in desire to eat and quantity of food to eat, the tendency of hunger ratings lower in IF2-P compared to IF1-P.
Intermittent vs. continuous energy restriction [106]	Headland et al, Australia (2019)	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 3 months, a total of eight visits. Participants were grouped based on gender, BMI, and age, randomized 1:1 to intervention groups.	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.
			Only 56%of participants finished the trial. The primary outcome was weight loss. Secondary outcomes were changes in body composition, weight loss, and glucose.	
IF and concurrent exercise [61]	Kotarsky et al, USA (2021)	21 participants with a BMI of 25 - 34.9 were randomly assigned to normal eating (NE) or time-restricted eating (TRE), resistance training, and aerobic exercise standardized for both groups for 8 weeks.	RCT. 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 NE with no differences.
IF on body weight, composition, vital signs in low-income women with obesity [107]	Puerza et al, Brazil (2020)	58 women were randomized to hypoenergetic diet and time-restricted diet for 12 months. 31 lost to follow-up.	RCT. 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.

Table 7. Role of IF in Obesity - *(continued)*

	Study, country, (year)	Sample size/timeline	Methods	Findings
IF: overweight older men and women [62]	Domaszewski et al, Poland (2023)	116 healthy, non-smoking participants assigned to time-restricted eating (TRE) or educational control participants for 6 weeks	TRE group was advised not to consume calories for 16 h/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 [67]	Maaloul et al, Tunisia (2023)	20 obese men regularly performing Ramadan diurnal intermittent fasting (RDIF) were randomized into two groups: 1) RDIF with concurrent training (RDIF-CT); 2) RDIF without training (RDIF-NCT) for 4 weeks.	RCT. 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-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- and post-intervention.
IF, weight loss [105]	Salis et al, India (2022)	32 overweight/obese adults were assigned consecutively to an IF plan and followed up for 3 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 [66]	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 restriction with high protein meal replacement group (HP) (n = 48); 12-week weight loss data analyzed	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 age, sex, weight, and body composition at 0 and 12 weeks, data on adverse events were also collected.	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 weeks compared to baseline. No serious adverse events were reported in the three groups.
IF 5:2 [68]	Witjaksono et al, Indonesia (2022)	50 participants, 25 allocated to the fasting group, and 25 to the control group for 8 weeks	Non-blinded 1:1 two-arm RCT, 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.

IF: intermittent fasting; RCT: randomized controlled trial; BMI: body mass index; ITT: insulin tolerance test; LDL-C: low-density lipoprotein cholesterol; HP: hypertension; HDL: high-density lipoprotein.

Author Contributions

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Data Availability

The data are collected from the studies published online, publicly available.

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