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# Ketogenic diet and intermittent fasting - impact on body weight and various diseases

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**Abstract:**

**Introduction and purpose:** Obesity affects every age group and is associated with many negative health effects. Various diets are used to remove excess body weight. Recently, popular became two diets - intermittent fasting and ketogenic diet.

**Material and Method:** This paper reviews various types of research documents published since 2018. Its main aim is to summarize the latest knowledge of ketogenic diet and intermittent fasting, including contraindications, side effects, impact on body weight and many diseases. It is also aimed to highlight the need for future research of the effects of both diets on various diseases and body weight reduction.

**Results:** Both diets may be effective in weight loss and show other health benefits. Both ketogenic diet and intermittent fasting have proven to be effective in weight reduction. In the case of intermittent fasting the biggest impact on weight loss is calorie restriction. Ketogenic diet is effective as a result of calorie restriction, increased gluconeogenesis and loss of free water through increased diuresis. They can be used in the prevention and treatment of many diseases, including cardiovascular disorders, neurological disorders or potentially cancer. However, they cannot be administered by everyone and may cause dangerous side effects.

**Conclusion:** Ketogenic diet and intermittent fasting are successful strategies for body weight reduction. Moreover, both of them may be used as an additional therapy for various diseases. However, patients should be under supervision.

**Keywords:** intermittent fasting, weight loss, ketogenic diet, cardiovascular diseases, glycemia

## INTRODUCTION

Obesity has become a global problem in recent years. This condition is extremely dangerous as it increases the risk of many diseases, including type 2 diabetes[1], hypertension, coronary heart disease[2], dyslipidemia[3] and many others. [4] Many types of diets are being used to reduce body weight. In recent years, the ketogenic diet and intermittent fasting have become very popular. [5,6] Intermittent fasting (IF) is a general concept of various programs that manipulate mealtime. It uses short-term fast to improve health and body weight. [7] The most popular types of IF include: alternate day fasting (ADF)- on fasting days no calories are consumed, modified alternate day fasting (MADF), including ADF 25%- on fasting days, 25% of the standard calorie requirement is allowed, 5:2 fasting- limiting or not taking in calories for 2 days a week, time-restricted eating (TRE)- limiting calorie intake to a few hours during the day. Based on the time of meals consumed, early TRE and late TRE are distinguished. In non-fasting periods calorie intake is usually not restricted. [8–10] The ketogenic diet is a diet in which amount of carbohydrates is limited to less than 50 g per day, typically 10-15 g [5], patient also consumes a normal protein contribution - 1.2–1.5 g/kg of ideal body weight or 1.0–1.2 g/kg of fat free mass, and the rest of the calories come from fat. [11] For instance, in a 2000 kcal per day diet, the carbohydrate allowance would amount to approximately 20 - 50 grams daily. [12] This restriction induces a systemic shift from glucose metabolism toward the metabolism of fatty acids yielding ketone bodies such as acetoacetate and β-hydroxybutyrate as substrates for energy production. [13]

Insulin secretion decreases significantly, leading the body into a catabolic state. As a result, glycogen stores are depleted, triggering metabolic changes and the body enters a state of ketosis. [12] In both ketogenic diet and fasting, beneficial effect to some extent is associated with the production of ketones. Mild ketosis of 1 mM develops after 12 to 14 hours of fasting. [14] However after 24–36 hours, *β*HB concentrations of 2-3 mmol/L are reached, which can rise to 6–8 mmol/L if starvation persists. [15] In the studies of the early TRE (eating for 6 hours, from 8 a.m. to 2 p.m.) morning ketone levels after 18-hour fast increased, as measured by β-hydroxybutyrate, by 0.03 ± 0.01 mM, causing them to reach a plasma concentration of 0.15 ± 0.6 mM. Additionally mean glucose levels were lowered in the night by 7 ± 2 mg/dl. [16] Nutritional ketosis (NK) is a target range of ketone bodies in the plasma from 0.5 to 4.0 mM, is augmented by exercise and fasting, may be maintained via a diet with restriction of combined protein and carbohydrate to 30% of daily energy expenditure.[17] It should also be added, that weight loss varies depending on the type and subtype of diet used. In a meta-analysis involving 1,768 patients and comparing different types of IF, ADF/MADF showed the highest range of weight loss- 0.77% to 12.97% in over 3 to 26 weeks, as compared with the other regimens. The TRE produced weight loss ranging from 0.95% to 8.60%, while the 5:2 diet ranged from 1.7% to 7.97% weight loss. [18]

In healthy participants, K-LCHF (ketogenic low-carbohydrate high-fat diet) for 3–12 weeks could reduce body weight by 3.68 kg (95% CI, -4.45 to -2.90) . In adults with overweight or obesity and/or metabolic syndrome, VLCKD for 4–6 weeks demonstrated a clinically meaningful weight loss of 9.33 kg (95% CI, -15.45 to -3.22, MCID threshold 4.40 kg). [19]

IF and KD, apart form body weight reduction, have a positive effect on many processes in the body, including carbohydrate and lipid metabolism. [20,21] They reduce inflammation, exhibit neuroprotection and improve mood. This makes them potentially an effective adjunctive treatment for many diseases, including cardiovascular disease, pre-diabetes, dementia and others. [22–27] KD may have a positive impact on health, but doctors and patients should be aware of its side effects and contraindications, which means that it is not a good choice for everyone. [5] The applications of KD are currently diverse and constantly expanding, with the most common indications being obesity and treatment-resistant epilepsy, and it is also gaining a role in the treatment of neurological disorders, cancer, type 2 diabetes, PCOS, intestinal microflora disorders, and chronic pain. [28] There is an "obesity epidemic" in the world, which has intensified during the pandemic, which is why patients are increasingly looking for solutions to lose excess weight. The World Health Organization (WHO) estimates that 39% of the population is overweight and 13% are individuals with obesity. It is alarming that the prevalence of overweight among children and adolescents has increased from 4% in 1975 to 18% in 2016. Obesity is now called a "silent killer" because it increases the risk of many diseases such as hypertension, dyslipidemia, type 2 diabetes, ischemic heart disease, gallstones, sleep apnea syndrome, or cancer. [4,29]

**AIM**

The purpose of this article is to provide an up-to-date overview of both types of diets and their impact on various health conditions. The article focuses on contraindications, side effects, impact on body weight and various diseases.

## MATHERIALS AND METHODS

Bibliographic research was conducted in March 2024 and updated in July 2024 and was limited to articles in English published in the last 6 years. Articles were identified using the PubMed search engine. Two searches were performed, the first containing the keywords "intermittent fasting" and "weight loss". Second using key terms: “ketogenic diet” and "weight loss". To avoid exclusion of important studies, studies were not restricted by type of publication or study design. The articles were selected on the basis of the corresponding abstract. Some publications were selected from the content of the searched publications.

## CURRENT STATE OF KNOWLEDGE

### 1. Ketogenic diet

KD is a diet in which the amount of carbohydrates is limited to less than 50 g per day, and at the same time the intake of fats is increased to ensure adequate energy supply. Typically, the patient consumes 1 gram of protein per kilogram of body weight, 10-15 g of carbohydrates per day, and the rest of the calories come from fat, which is consumed in any amount, which puts the body into a state of ketosis.[5] Under normal circumstances, the body mainly uses carbohydrates to produce energy, and when the body has too little of them during KD, insulin secretion is reduced. Initially, stored glucose in the form of glycogen is available, but after three to four days it is depleted. In this situation, fat becomes the most easily available, and its breakdown into free fatty acids provides the raw material for the production of ketones in the liver. Importantly, in physiological ketosis there is no change in blood pH compared to pathological ketosis, in which blood pH is lowered. [5,29]

### 1.1 Contraindications

The first contraindication is advanced renal failure, because the excretion of ketones in urine is impaired, and the acidosis present in the body creates a high filtration load for the kidneys. Type 1 diabetes is probably the best described contraindication due to the increased risk of diabetic ketoacidosis and hypoglycemia. The use of KD in the elderly is discouraged for several reasons. Firstly, this diet causes increased urination resulting in a drop in blood pressure and dehydration, which leads to an increased risk of falls. Secondly, this diet usually requires the use of supplements that patients forget about, which can cause heart rhythm disturbances and vitamin deficiencies. Limited mobility in seniors causes an increased risk of pressure sores and impaired wound healing. [28] Other contraindications include a history of mental disorders, alcohol and other psychoactive substance abuse, liver failure, unstable angina and a recent heart attack. [4] Selected contraindications are summarized in the figure number 1.

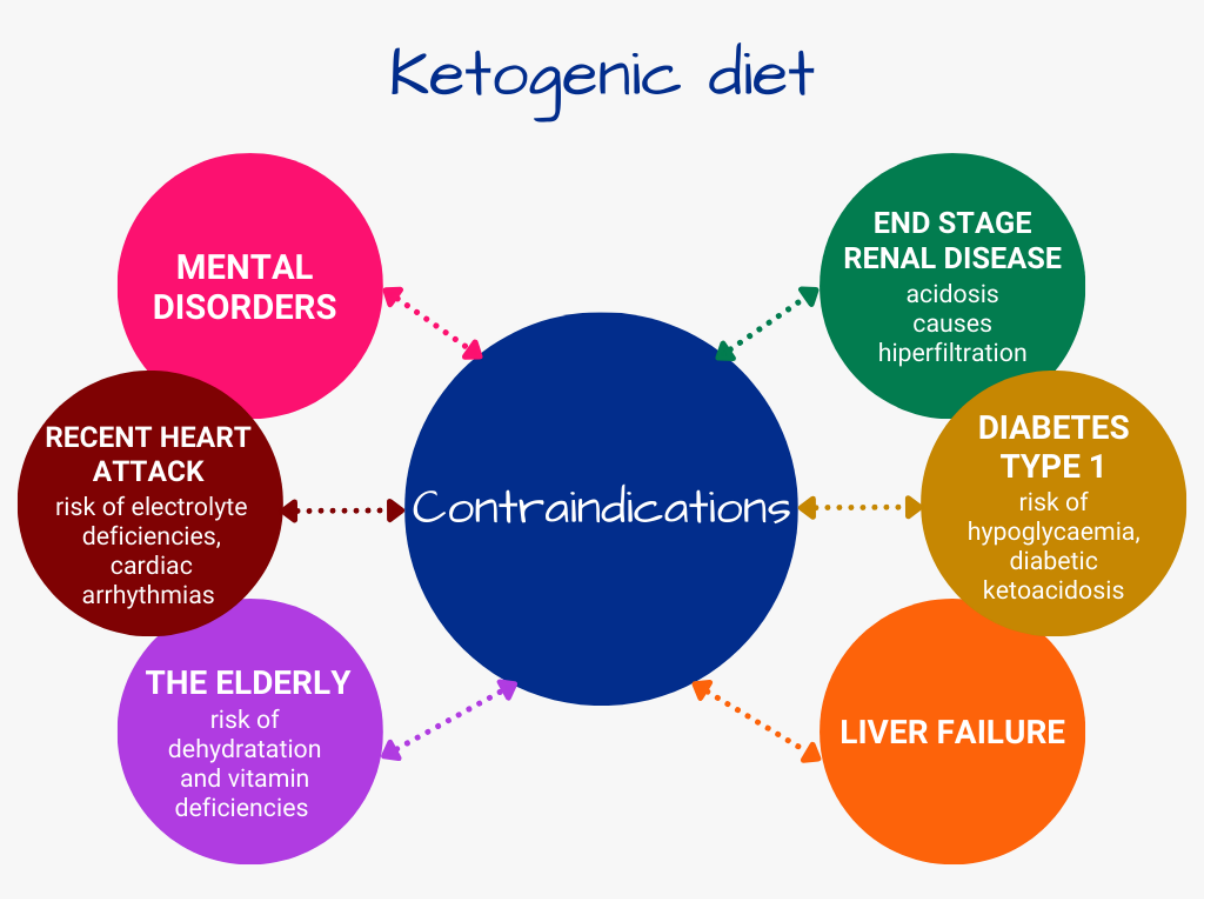

Figure 1. Contraindications of the ketogenic diet. [1,20]

**1.2 Side effects**

Possible effects of the ketogenic diet include:

1 Dehydration - dry mouth, headache, dizziness, orthostatic hypotension and visual disturbances. For this reason, adequate water consumption (at least 2 liters of sugar-free fluids per day) is mandatory.

2 Transient hypoglycemia may be a complication of VLCKD, usually in the early stages

3 Temporary lethargy may occur in the first days of the protocol and occurs as the body switches from burning carbohydrates to burning fat for energy.

4 Halitosis can occur during VLCKD and is caused by an increase in acetone levels

5 Gastrointestinal disturbances including nausea/vomiting, diarrhea or constipation. They are often associated with poor diet tolerance, which results in significant resistance to the ketogenic diet (fat intolerance) and even weakening its effectiveness.

6 Urolithiasis - deposits consist mainly of uric acid, calcium oxalate or a mixture of calcium oxalate and calcium phosphate/uric acid. The cause of urolithiasis is chronic acidosis, dehydration and fat absorption disorders

7 Cholelithiasis - excess fats and rapid weight loss increase the risk of developing gallstones. The bile becomes oversaturated with cholesterol, which leads to cholesterol crystallization and the formation of stones

8 Hyperuricemia - serum uric acid concentration increases in people following a ketogenic diet providing less than 900 calories a day. [4,30]

**Use of keto in pediatric patients:**

KD has long been used as a therapy in children with epilepsy due to its ability to reduce the frequency and severity of seizures, the diet has also been proposed for other diseases such as cancer, obesity and genetic neurological and metabolic disorders (glycogen storage diseases, mitochondrial disorders, Prader - Willi, Rett, Angelman syndromes, gliomas, neuroblastoma, myoclonic epilepsy, drug-resistant epilepsy, autism spectrum disorder etc.). In addition to its potential benefits, KD may pose difficulties in use in children and adolescents, for example in long-term dietary adherence, due to the limited variety of foods consumed. In addition, another difficulty is the side effects of the diet such as nausea, constipation, fatigue, dehydration and electrolyte disorders. Scientists are investigating the impact of KD on children's growth, but the studies produce conflicting results. Vitamin and mineral deficiencies have been described among patients, therefore supplementation may be recommended (folic acid, calcium, selenium, copper, vitamin D3, or magnesium). The use of a diet in children requires constant supervision of caregivers and health care workers due to possible complications and nutritional deficiencies, therefore patients should be subjected to frequent medical check-ups. [31] It has now been proven that KD can be safe and effective in the treatment of epilepsy even in infants, and ketosis can be achieved and maintained more easily than in older children. The diet significantly reduces the number and severity of epileptic seizures. Ketogenic formulas for infants are becoming more and more available, and it is best to start KD therapy before introducing solid foods into the diet. Breastfeeding is usually replaced with ketogenic formulas, but sometimes you can supplement the diet with breast milk after calculating the amount of carbohydrates. [32]The main source of energy for a baby in mammalian milk is fat, and carbohydrates constitute less than 12% of available nutrients. This proves that brain development after birth depends more on energy from ketones than from glucose. [33]

### 1.3 Effect on body weight

There are various theories explaining weight loss during KD use. When carbohydrate consumption is limited, insulin secretion decreases, which leads to lipolysis of adipose tissue. Additionally, in the absence of glucose in the blood, the body increases gluconeogenesis to deliver glucose to the brain. This process requires large amounts of energy. There is also a loss of free water through increased diuresis associated with high levels of ketones in the blood, rather than actual fat loss - especially in the initial stages. [5]

It is also hypothesized that weight loss is due to direct suppression of appetite and early weight loss. During periods of fasting, or when carbohydrates are in short supply, the ketone bodies acetoacetate, βeta-hydroxybutyrate (βHB) and acetate are synthesized from free fatty acids, as an alternative source of energy. The metabolic state of nutritional ketosis is usually defined as a plasma βHB concentration ≥ 0.5 mmol/l.[34] Evidence shows that the secretion of the hunger hormone ghrelin is blunted under ketogenic conditions. Several studies in females show correlation between the plasma concentration of βHB measured in a fasted state and changes in markers of appetite in participants who have lost weight through KD. There is a negative association between βHB and changes in basal ghrelin concentrations and a positive association between βHB and changes in postprandial GLP-1 and CCK concentrations.

Moreover, evidence points that exogenous ketones have the ability to suppress appetite and reduce ghrelin secretion, suggesting that ketone bodies might have a direct effect on appetite. [35]

Overall, there is evidence from animal studies that intracerebroventricular infusion and subcutaneous injection of β-hydroxybutyrate reduce food intake. Data in humans come from evidence of reductions in appetite following consumption of a taste-matched ketone ester drink compared with a dextrose drink. In response to consumption of the ketone ester drink, β-hydroxybutyrate levels increased, the onset of hunger was delayed and plasma ghrelin levels were reduced. Moreover, β-hydroxybutyrate circulating concentrations were inversely correlated with change from baseline in hunger and desire to eat, and positively correlated with fullness. [36]

Ketogenic diets may normocaloric (isocaloric/eucaloric KD) or with a reduced energy intake (low calorie or very low calorie ketogenic diet – VLCKD) but, in both cases, they should be rich in fats, adequate in protein and low in carbohydrates, to produce ketosis. VLCKD can be used continuously for up to 12 weeks in order to loose weight, but it must be performed under medical surveillance.[4] This type of diet achieves the desired weight in less time than conventional low-calorie diets. Usually, an average weight loss of 1–1.5 kg per week is achieved with variations due to gender, body type and individual physical activity. [37] In a controlled study involving 20 participants receiving a nutritional intervention with VLCKD, a significant improvement in anthropometric and biochemical parameters was observed after eight weeks of therapy. This included a reduction in BMI, LDL-C, triglycerides, insulinemia, and liver transaminases. Additionally, it was reported that VLCKD also reduced inflammation. Isocaloric ketogenic diets are used in therapy of various diseases such as drug-resistant epilepsy. [38]

### 1.4 Effect on various diseases

#### Cardiovascular diseases

Cardiovascular diseases are the most common cause of death in the world. It is common knowledge that diet also influences their occurrence. Due to the negative opinion about fats in terms of the risk of developing cardiovascular diseases, there is much controversy regarding the use of KD in such cases. Many animal and human studies, both observational and experimental, have shown conflicting results regarding effects on cardiovascular health. However, recent scientific evidence suggests that this may be a promising direction for further analysis. Ketone bodies have a cardioprotective effect in heart failure patients with reduced ejection fraction because they improve the metabolic state of the heart. [20] A ketone body called 1,3-butanediol (BD) is converted into BOHB, which increases the synthesis of the NO-producing enzyme - nitric oxide synthase. Thanks to this, KD can promote vasodilation and increase blood flow through the heart muscle. BOHB has an anti-inflammatory effect on the heart by suppressing the Nod-like receptor protein 3's (NLRP3's). In addition, patients eliminate pro-inflammatory simple sugars from their diet. Well-balanced meals are rich in omega-3 acids, which beneficially modulate the immune system. In addition, KD lowers the heart rate due to weight loss and regulating the activity of the sympathetic nervous system by reducing the secretion of cortisol in saliva and inhibiting the hypothalamic-pituitary-adrenal axis. [20]

Studies on the impact of KD on the lipid profile of patients show divergent results. The beneficial or adverse effect of the diet depends on the quality of the fats consumed. Differences in the composition of KD may affect its action. Traditional KD is high in saturated fats (SFA), which come from cream, butter, and bacon, which results in hyperlipidemia. Replacing SFAs with polyunsaturated fatty acids (olive oil, avocado, fish) can prevent this. Some analyzes have shown that KD reduces the concentration of total cholesterol, LDL-C and triglycerides and increases the concentration of HDL-C in the serum. However, other studies have shown a reduction in only triglycerides and total cholesterol, or a greater reduction in triglycerides but an increase in LDL-C and HDL-C. The above data make it impossible to draw clear conclusions about the impact of KD on the lipid profile. KD may also lower blood pressure because it leads to weight loss, inhibits the sympathetic nervous system, increases diuresis, and has an anti-inflammatory effect on the vascular endothelium. [20,29]
In summary, KD has controversial effects on the cardiovascular system, but many studies have revealed its potentially positive preventive effects, which are mainly due to weight loss. More research is needed to clearly assess the benefits of its use.

**Neurological diseases**

- **Epilepsy resistant to treatment**

The ketogenic diet (KD) has been used to treat epilepsy for over 100 years. Despite many studies, it is still unknown why a high-fat diet is beneficial in the treatment of this disease. The hypothesis explaining this phenomenon is that ketones are the main source of energy for brain development in fetus and infancy. Repairing brain tissue in epilepsy requires a high reservoir of energy, so re-implementing ketone body-based metabolism may enable brain networks to more effectively regenerate damage. KD affects neurotransmission at synapses and can improve neuronal and glial structure, and also regulates CNS homeostasis. [30]
Many epilepsy patients have been shown to have seizures that stop even after they stop eating the diet. These findings suggest that KD combines anticonvulsant and disease-modifying effects. [39] Ketones may be a more efficient source of energy for the brain than glucose, they increase the number of mitochondria in neurons and glial cells. An increase in the amount of energy produced by mitochondria causes the stabilization of the resting potential of neurons and their hyperpolarization, which makes it more difficult to experience an epileptic seizure.[40] Additionally, an increase in ATP production improves neuronal homeostasis and resistance to damage during seizures. Additionally, low or stable glucose levels reduce susceptibility to seizures. KD leads to an increase in GABA levels and a decrease in glutamate levels in the brain. It reduces the production of ROS, increases the amount of glutathione, which protects mitochondrial DNA against free radical damage that is produced during seizures. Recent evidence suggests that the kynurenine pathway is involved in neuroprotective and anticonvulsant effects. Recent reports indicate the possible role of kynureninic acid, which is suspected of having neuroprotective and antiepileptic effects. [30] Epilepsy patients have a disorder of the intestinal microflora, which causes reduced production of short-chain fatty acids and neurotransmitters such as GABA and serotonin. KD has been shown to have a beneficial effect on the intestinal microbiome and thus support antiepileptic effects. [40]Currently, BD can effectively treat epilepsy in people from infancy to adulthood. It is mainly used in forms that are resistant to treatment.

The diet often allows you to reduce or discontinue medications, and a significant reduction in the frequency of seizures is observed. KD also affects neurobehavioral development, cognitive functions and sleep quality by prolonging the REM sleep phase. [30] KD therapy can also be considered in refractory epileptic states as an adjuvant treatment. Most patients received KDT enterally, usually using a nasogastric tube or percutaneous endoscopic gastrostomy, and in some cases intravenously. [41]

- **Migraine**

Migraine is one of the most persistent neurological diseases in the world; headaches impair the quality of life of patients and may cause cognitive impairment in older people. It has been proven that some dietary ingredients such as chocolate, cheese, alcohol or caffeine trigger migraine attacks. Additionally, overeating, starving yourself, eating dinner too late, or snacking at night have a negative impact on your symptoms. For this reason, scientists are looking for an appropriate anti-migraine diet, including the ketogenic diet, but its effectiveness has not yet been proven due to divergent research results. [42] Ketone bodies produce more ATP than an equivalent amount of glucose, e.g. 100 g of glucose is equivalent to 8.7 kg of ATP, while 100 g of acetoacetate produces 9.4 kg of ATP. Energy deficiency in the form of ATP, as well as increased demand for it, are important components of the pathogenesis of migraine. Reactive oxygen and nitrogen species are then produced, which damage brain structures. When using KD in treatment, it is important that ketone bodies can cross the blood-brain barrier and provide energy to the CNS, as well as perform antioxidant functions that reduce oxidative stress. [42] Migraine is an inflammatory disorder, characterized by a sterile meningeal neurogenic inflammation which stimulates trigeminal afferent nociceptive neurons innervating intracranial meninges and related large blood vessels. Moreover it
activates mast cells and macrophages which in turn release cytokines, serotonin, histamine and proteases. KD protects neurons because of its anti-inflammatory potential. [43]
Due to the above properties of ketones, it is indicated that KD may reduce the number and severity of migraine symptoms, but so far inconsistent research results have been obtained.

- **Parkinson's disease**

Parkinson’s disease (PD) is a common neurologic disorder. It is a progressive, neurodegenerative disease manifested by motor and nonmotor symptoms. It is a significant cause of disability in the world, affecting at least 53 million people globally. The prevalence in industrialized countries is estimated to be 0.3%. PD is rarely seen in patients under 40 years of age, but the incidence increases with age. Symptoms include resting tremor, bradykinesia, postural instability, and rigidity. [44]
The main factor responsible for the development of symptoms is the degeneration of dopaminergic neurons in the substantia nigra, which are involved in transmitting dopamine through the basal nucleus and striatum. Their damage leads to impaired transport of this neurotransmitter, which results in movement disorders. The pathogenesis involves alpha-synuclein deposits forming Lewy bodies. KD may be a complementary therapy to the main drug used in PD, i.e. levodopa. Studies show that ketones significantly improve the bioavailability of L-DOPA.

Moreover, β-hydroxybutyrate has a neuroprotective effect on dopaminergic neurons. This is associated with increased mitochondrial respiration and ATP production. KB also reduces the number of free oxygen radicals.
It is known that the microflora of PD patients differs significantly from that of healthy people and is characterized by a low number of Prevotellaceae and an increased number of Enterobacteriaceae, and the ketogenic diet reverses these proportions. [45] Considering the wide range of effects on aspects of PD and the potential therapeutic possibilities of the ketogenic diet, further research in this area seems to be very necessary.

- **Multiple sclerosis**

Multiple sclerosis (MS) is the most common autoimmune disease of the central nervous system in young adults that may lead to progressive disability. It is characterized by neuroinflammation, demyelination, gliosis, and neuronal loss. Diet is currently recognized as one of the risk factors and may be used in the treatment. There is no cure for MS, but several immunomodulatory therapies are available that may slow disease progression, therefore there is a need for complementary therapies such as specific diets. Research indicates that, due to the pathogenesis of MS, the ketogenic diet may provide benefits through its anti-inflammatory, antioxidant, neuroprotective potential. [46,47]
Insulin resistance seems to be more common in MS patients than in healthy controls.
Elevated serum levels of the pro-inflammatory cytokine IL-17 in MS patients may contribute to the impaired glucose and insulin metabolism. The cerebral glucose hypometabolism that occurs in MS patients is thought to reflect mitochondrial dysfunction in neuronal cells. Studies have demonstrated increased markers of oxidative stress and decreased compensatory antioxidative capacity in MS patients. KD reduces carbohydrate intake and it has been suggested that the resulting ketone bodies facilitate the regeneration of demyelinated axons. This diet may slow disease progression, improve motor disability, reduce hippocampal atrophy, reverse lesions and suppress inflammatory cytokines and reactive oxygen species.Recent studies have shown that gut dysbiosis can also occur in MS patients. KD may positively affect the gut microbiota by enhancing gut microbial diversity. [46]
Studies show a reduced activation of microglia and reactive astrocytes while following KD, as well as an enhanced differentiation and maturation of oligodendrocytes. These effects have a positive impact on alleviating neuroinflammation in MS patients. [47]

- **Dementia**

Dementia (a major neurocognitive disorder) is one of the most common troublesome diseases, and its prevalence is constantly increasing. For this reason, the condition remains an urgent public health priority, affecting over 50 million people worldwide, with the most common form being Alzheimer's disease. [48] Mitochondrial dysfunction, the antioxidant system, the anti-inflammatory response, anti-apoptotic signaling, and the gut-brain axis are the main pathophysiological features of neurodegenerative diseases. [49] Currently, it is believed that many cases can be prevented or their development delayed. Current treatment methods cannot reverse or completely stop the progression of dementia; their action is based on alleviating the symptoms of the disease. Therefore, preventive methods are being sought, and it has been proven that diet can delay the occurrence of cognitive disorders.

The pathogenesis of dementia involves an inflammatory and metabolic component, therefore the use of a ketogenic diet may bring positive effects thanks to the increased ATP level, anti-inflammatory and antioxidant properties already mentioned in the previous paragraphs. Ketones reduce the amount of free radicals that damage the CNS. Focal reductions in glucose utilization are present in the brains of sick people. Because neurons prefer ketone bodies for energy metabolism, ketone uptake during dementia is not reduced like glucose uptake, so they may be an alternative source of energy. Obesity increases the risk of cognitive disorders, therefore weight loss while using KD contributes to the prevention of this disease. [50] In addition to its antioxidant and metabolic effects, KD has anti-apoptotic activity, which contributes to neuroprotection. Reduced expression of pro-apoptotic factors such as clusterin and caspase-3 was detected in KD-fed animals. Moreover, KD inhibits apoptosis of neuronal cells by decreasing the level of Bax expression and in hippocampal cells by inhibiting the AMPK pathway and HSP70 expression. [49] In Alzheimer's disease, brain energy metabolism is impaired. Compared to healthy controls, patients show lower levels of insulin signaling in the brain and fewer receptors, leading to CNS insulin resistance. Neurons also show reduced numbers of mitochondria, many of which show reduced activity of the citric acid cycle and respiratory chain, leading to a decline in energy production. The best results were achieved when KD was used for at least 12 weeks, which resulted in improved cognitive abilities of people with AD. [48] Scientists point out that it is difficult to follow the diet in people with cognitive disorders, so its use must be under constant supervision of caregivers. You should also pay attention to the side effects of the ketogenic diet, because dementia usually affects elderly people, you need to monitor fluid balance and electrolyte disorders, which can be dangerous to life and health. [50]

**Psychiatric diseases**

- **Mood disorders**

Mood disorders are one of the most common psychiatric diseases. Major depressive disorder (MDD) is estimated to affect 3–17% of all adults at some point in their lives, and bipolar disorder (BD) affects 1-3% of the general population. A reliable epidemiological report reports that mental illness causes the loss of 7.3–10.2 years of life. Additionally, it sometimes happens that patients are resistant to classical treatment, which is why new therapies and complementary treatments are constantly being sought, for example in the form of a specific diet that alleviates or prevents symptoms. The pathogenesis of the disorders is complex, their occurrence is influenced by, among others, the level of neurotransmitters and chronic, low-grade systemic inflammation. It has been proven that obesity and metabolic syndrome play a significant role in the pathogenesis of mood disorders. In order to lose weight in patients with depression or bipolar disorder, the ketogenic diet, the Mediterranean diet and intermittent fasting are considered. [24]

The literature reports that KD may affect neurotransmitters such as dopamine, serotonin, and norepinephrine. Scientists found changes before and after KD application for homovanillic acid (HVA) and 5-HIAA, the concentrations of which in the cerebrospinal fluid were reduced during dietary treatment, suggesting that KD is associated with dopaminergic and serotonergic effects (changes in kynurenine metabolism).

In addition, ketones have the above-mentioned anti-inflammatory effect, which has a beneficial effect on mood disorders, and currently used pharmacological drugs used in the treatment of depression also have this property. [23,24] Currently, there are no randomized clinical trials describing the impact of KD on mood disorders, but it is a desirable topic for future analyses.

**Cancer and other diet induced changes**

- **Cancer**

Cancer remains one of the leading causes of death in the world, and its incidence in the population is constantly increasing. Their occurrence is influenced by various factors, including tobacco, but also lifestyle, obesity and diet. Diet has been estimated to account for approximately 30% of the attributable cancer risk. Particular attention is paid to the negative impact of a high-carbohydrate diet, which causes metabolic and hormonal disorders that favor the development of cancer. It has been proven that 40% of all cancers are related to overweight and obesity, especially cancers of the liver, endometrium, esophagus and kidneys. The use of a ketogenic diet in the prevention or treatment of cancer as a complementary procedure aims to deprive cancer cells of their main source of energy, i.e. glucose. This causes chronic metabolic stress on the tumor. [22] Additionally, some cancers are unable to metabolize ketone bodies due to mitochondrial dysfunction and decreased enzyme activity. Another benefit is a decrease in the levels of insulin and insulin-like growth factor, which stimulate the proliferation of cancer cells. However, available preclinical evidence indicates that the use of KD as an adjuvant anticancer therapy strongly depends on the type of cancer and its genotype. [22,51] KD has an anti-inflammatory effect, which creates an unfavorable environment for tumor growth, suppresses the NLRP3 inflammasome and reduces inflammatory factors such as TNF-α, IL-1, IL-6 and IL-18 and prostaglandin E2. [22] The effect of KD on cancer cachexia is ambiguous. Some studies show that it can worsen the condition, while others show that it reverses it. The quality of the fats consumed is important (polyunsaturated fats, omega-3 are mainly recommended). KD may be a good choice for cancer treatment in obese patients. [52] KD can also sensitize cancer cells to chemotherapy and has anti-angiogenic effects, thus limiting tumor growth, but the exact mechanisms of this phenomenon have not been characterized. Studies indicate that KD promotes cell apoptosis. Ketones may affect gene expression, BHB inhibits histone deacetylases (HDAC), which remove acetyl groups from lysine residues on histones and other proteins - transcription factors, enzymes. Deacetylation of histones loosens the tight packing of DNA, which allows gene transcription, while deacetylation of transcription factors or enzymes can affect their activity. [22] To date, evidence from randomized, controlled trials is lacking, but it is needed to find out whether KD will benefit cancer patients. The data are mainly based on single case reports and a few preliminary clinical studies in small study cohorts and on preclinical studies in animals. [51]

- **Microbiome**

Microbiota acquired at birth develops in parallel as the host and maintains its temporal stability and diversity through adulthood until death. Microbiome is responsible for various functions in human body such as metabolic, protective, structural, and neurological role. It is estimated that dysbiosis has a significant impact on the occurrence of many diseases. Moreover, studies show that diet may regulate the diversity of symbiotic bacteria. [53]

Currently, the relationship between KD and the intestinal microbiome is being sought by examining how diet affects the composition and characteristics of microorganisms, but there is still not enough research. After applying the diet to patients, an increase in the number of beneficial bacteria Akkermansia Muciniphila and Lactobacillus was observed in the intestinal microbiota, which have the ability to produce short-chain SCFA fatty acids. In addition, a reduction in the number of pro-inflammatory microorganisms such as Turicibacter was observed. The composition of a high-fat diet is also important; for KD to have a beneficial effect on the microbiome, it must contain a large amount of polyunsaturated acids, because a recent systematic review concluded that diets rich in saturated fatty acids have a negative effect on the intestinal microflora. [54]
Furthermore, Desulfovibrio, which is considered a harmful bacterial genus as it produces H2S that causes damage to the intestinal mucosal barrier, appeared reduced after KD treatment. [55]

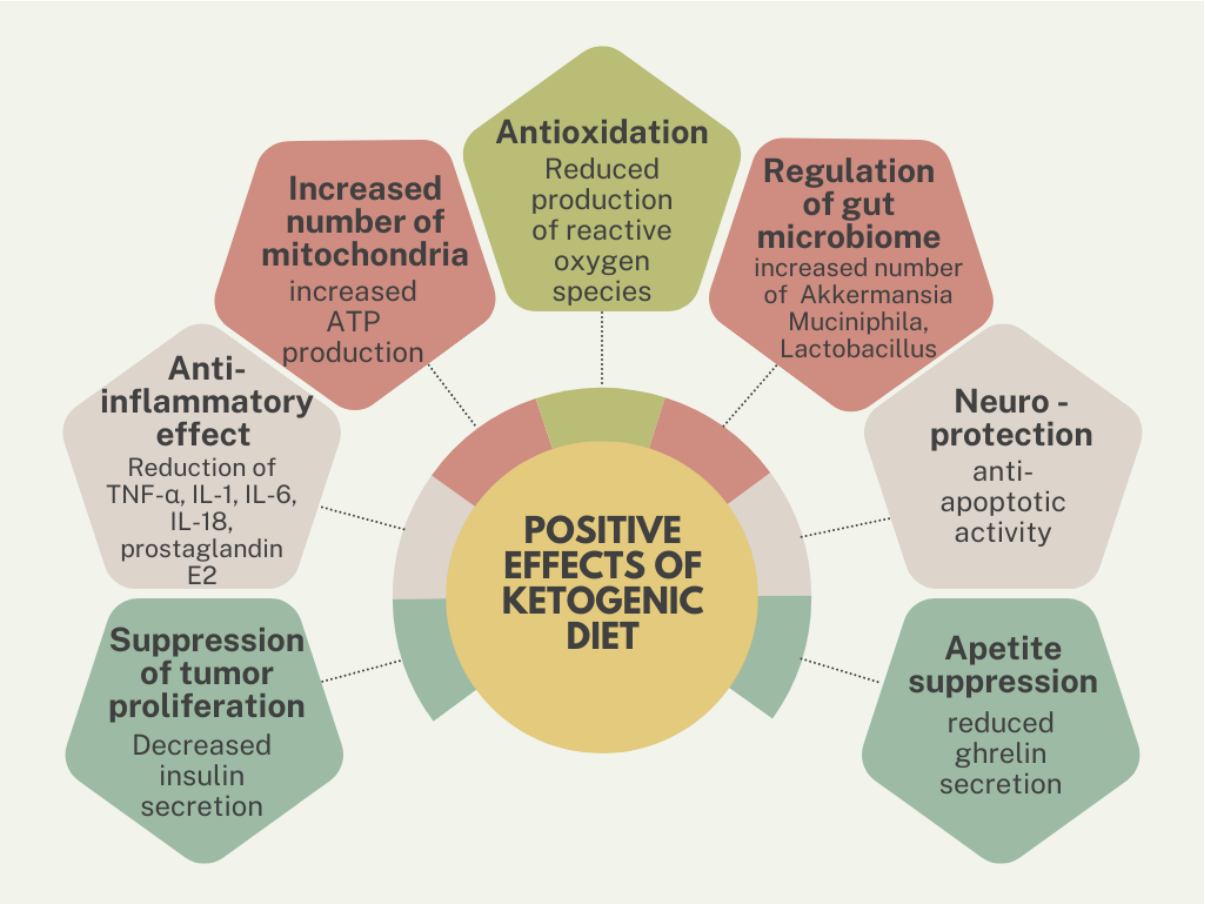

Figure 2. Positive effects of the ketogenic diet.

**2. Intermittent fasting (IF)**

Intermittent fasting has become very popular in recent years due to its clinically significant impact on weight loss. [6] Some people call it "the next big weight loss fad", but the fast has been known for a long time. It is part of many cultures and religions, including Latter-Day Saints (LDS) religious practice. [25] A well-studied example of fasting is the one-month long Ramadan. [56] Intermittent energy restriction is an interchangeable term for Intermittent fasting. [18]

Intermittent fasting can take many forms. The description of the most frequently used forms of IF is presented in table 1.

| Form | Specification |
|---|---|
| Alternate day fasting (ADF) 0% | on fasting days no calories are consumed, on non-fasting days calorie intake is not limited in any way, i.e. ad libitum |
| Modified alternate day fasting (MADF), w tym ADF 25% | during fasting days, 25% of the standard calorie requirement is allowed |
| 5:2 fasting | limiting or not taking in calories for 2 days a week, on the remaining 5 days the intake of calories is not limited |
| time-restricted feeding (TRF) | limiting calorie intake to a few hours during the day, usually a period of 8 to 10 hours |

Table 1. The most commonly used forms of IF. [18,57]

During fasting, triglycerides are mobilized as substrates for oxidative metabolism due to glycogen depletion. Clear boundaries between periods of macronutrient accumulation associated with food intake and oxidation are associated with greater metabolic flexibility compared to constant nutrient flows with time-indefinite eating. Increased metabolic flexibility is associated with weight loss, improved insulin sensitivity and fat turnover.[18]

## 2.1 CONTRAINDICATIONS

Intermittent fasting is considered a safe diet. It does not cause disturbances in energy levels and is not associated with increased inappropriate eating behaviors. [9] This is, however, a diet that requires considerable control. Emotions, the desire to eat or hunger must be controlled. [58]

IF is not recommended for people with reactive hyperglycemia or taking antidiabetic drugs because it may lead to serious, even life-threatening, hypoglycemia. In both young and older people, hypoglycemia increases the risk of a cardiovascular event [59] and is associated with deterioration of cognitive and behavioral functions (confusion, coordination disorders, blurred vision) and worse mood (anxiety, nervousness). [58] IF also increases the risk of ketoacidosis in diabetics. [59]

IF is contraindicated in pregnant women because long periods of hyperketonemia in pregnant women have a negative impact on the fetus. They are associated with fetal developmental defects, impaired neurophysiological development and even stillbirth. Likewise, IF is contraindicated during breastfeeding. Ketogenesis increases after a short period of fasting and may be associated with the occurrence of ketoacidosis in a breastfeeding woman. [10] Intermittent fasting should also not be used in children and people performing heavy physical work. Individuals using intermittent fasting are advised to seek advice from doctors or dietitians to avoid side effects. [59]

## 2.2 SIDE EFFECTS

In the first days of fasting, possible side effects include headaches, muscle pain, sleep problems and sleep disturbances. Their occurrence is correlated with previous lifestyle, general health and psychological predispositions. [60] In the case of short-term fasting, you may also experience slight dizziness and negative emotions: depression, irritability, fatigue, feeling of tension or anger. Drinking plenty of water may be effective in preventing headaches. [26] Eating only in the evening, which occurs among other things in late TRE, can lead to disrupted circadian rhythms. Delayed meal intake can induce a weakening of the diurnal cortisol rhythm and a disturbance in glucose metabolism, including an elevation of 24-hour glucose levels. [61]

## 2.3 Effect on body weight

Of all types of IF, the highest rate of weight loss occurs in ADF/MADF. [18] Studies of obese people have shown a decrease in body weight when using IF, regardless of overall caloric intake. The decrease in body weight ranged from 0.8 to 13% of the original weight, the decrease in BMI was on average 4.5%, and the waist circumference decreased from 3 to 8 cm in the case of studies lasting more than 4 weeks. Another study highlighted the greater effectiveness of ADF than 16/8TRF in reducing body weight and BMI. [62] A study comparing IF combined with high-protein intake with caloric restriction (CR) showed greater effectiveness of IF in weight loss compared to calorie restriction. [21] Most studies, however, indicate a comparable effect of both types of diet. [18,63] In a twelve-month study comparing the effectiveness of IF, the Mediterranean diet, and the Paleo diet in overweight people, the highest effectiveness in weight loss was achieved by fasting people. [64] During IF, fat tissue is mainly lost. [65]

When losing body weight during fasting, attention should be paid to the decrease in appetite and the influence of intestinal microflora. The microbiome has a proven impact on body weight regulation. Its content at the beginning of the diet affects the achieved weight loss and waist circumference. For example, higher baseline abundance of Subdoligranulum variabile is associated with greater weight loss and greater improvement in insulin sensitivity, and higher baseline abundance of Slackia Coriobacteriaceae and other unclassified members of this bacterial family predicts greater loss of waist circumference and has been shown to have a beneficial effect on Roux-gastric bypass. en-Y in people with type 2 diabetes. [45] The content of the microbiome also changes during fasting. 16 types of bacteria have been shown to change in abundance. [66] A decrease in the abundance of the genus Coprococcus 3 is associated with greater weight loss, while an increase in the genus Phascolarctobacterium is associated with a greater reduction in waist circumference. During intermittent fasting, the abundance of Akkermansia bacteria increases compared to constant caloric restriction. A. muciniphila in animal models has been causally associated with reducing body fat mass, reducing inflammation of adipose tissue and improving glucose homeostasis. Akkermansia also produces acetate, a possible primary mediator of gut microbiota-dependent changes in adipose tissue composition, including Beiging, a process by which white adipose tissue assumes a brown adipose tissue phenotype. Altering the phenotype of adipose tissue is important in increasing insulin sensitivity and resting energy expenditure. [67]

It has been speculated that intermittent fasting may provide metabolic benefits independent of energy balance by initiating fasting-mediated mechanisms, however, no such phenomenon has been proven in studies.

In a three-week study of healthy, lean individuals comparing the effect of 24-hour fasting combined with reduced caloric intake to no caloric restriction, only the group of subjects with reduced caloric intake showed a decrease in body weight, including a decrease in fat mass. [68] In another study early time-restricted eating plus daily calorie restriction by obese individuals for 39 weeks resulted in weight loss comparable to only daily calorie restriction of ~35% of calories (~ 5kg body weight loss in both groups). [69]

Circadian rhythms control many aspects of physiological function over a 24-hour cycle, including sleep and wakefulness cycles, heartbeat, hormone production and secretion, body temperature and blood pressure. Circadian rhythms are controlled in the central nervous system by the suprachiasmatic nucleus of the hypothalamus (SCN), but peripherally by cells distributed throughout the body. The SCN is innervated internally by light-sensitive retinal ganglion cells, making it use light as a cue to adjust circadian phase. In addition, a cellular network within the SCN provides it with autonomy by resisting molecular and neuronal oscillations. [70] Circadian rhythms organize metabolism into daily 24-hour cycles by, among other things, temporarily separating opposing metabolic processes and anticipating repeated feeding and fasting cycles. Such activities lead to improved metabolic efficiency. Circadian rhythms of insulin, glucose, glucose tolerance, energy expenditure, lipid levels and appetite are known. Some of these peak in the biological morning or around noon, suggesting that the most optimal time of day for food intake is earlier in the day. [71] With this in mind, early and late TREs can be compared. Early TRF (feeding between 8:00 am and 2:00 pm) for 4 days noticeably increases serum cortisol levels in the morning. In another study, 5-week early TRF (6-hour feeding with lunch before 3:00 pm) in pre-diabetic subjects improved the pancreatic β-cell response to glucose, as demonstrated by an oral glucose tolerance test. [70] A meta-analysis of 12 randomized controlled trials showed that both early TRE and late TRE resulted in a similar degree of weight loss. Also, both forms of TRE resulted in improvements in insulin resistance; however, better results occurred in the early TRE group. In addition, only the early TRE group showed significant benefits in glycemic metabolism (including a more significant effect on improving HOMA-IR) and blood pressure.[8]

Additionally, increasing energy intake early in the day can be hypothesized to increase subjective energy levels, potentially translating to higher levels of physical activity early in the day.[69]

## 2.4 EFFECT ON VARIOUS DISEASES

According to research, reducing the risk of comorbidities and achieving clinically significant improvement in health (decrease in blood pressure, glucose and triglyceride levels) is possible if weight loss is 5 to 10% within 6 months. [72]

### Cardiovascular diseases

- **Many studies have confirmed the positive effect of IF on important risk factors for cardiovascular diseases: carbohydrate metabolism, lipid metabolism, atherosclerosis and blood pressure. [59]**

IF with the appropriate amount of protein consumed has a positive effect on the cardiovascular system, reducing cardiovascular risk by: reducing the level of total and low-density lipoprotein cholesterol, triglycerides, [21] systolic and diastolic blood pressure. [59]

IF also slows the development of atherosclerotic plaques by reducing inflammatory markers, including C-reactive protein, Interleukin 6 and homocysteine. The lipolysis of triglycerides in chylomicrons and the production of mature, spherical HDL cholesterol particles are increased. [26] The secretion of adiponectin from adipocytes is also increased. The level of adiponectin in plasma decreases in the course of diabetes, insulin resistance, coronary diseases and atherosclerosis. It is a collagen-like protein that has anti-inflammatory and anti-atherosclerotic effects by inhibiting the adhesion of monocytes to endothelial cells. An inverse correlation has been proven between body weight and adiponectin levels. [59] IF affects the level of satiation. Compared to CR, IF resulted in a 42% decrease in the desire to eat. [21] There was also a greater reduction in hunger when fasting two days a week compared to one day. [73] Other studies, however, have shown even an increased risk of craving in IF compared to CR. [60] Studies primarily conducted on LDS who regularly fast have shown a 35% reduction in the risk of coronary heart disease. [25]

- **Glycemia**

-IF also has a positive effect on glycemia in obese patients. [60] It is an effective form of therapy for prediabetes. [74] Also for patients with type 1 diabetes, IF is an effective and safe method of reducing body weight and the amount of hemoglobin A1c in the blood, although the amount of research on this subject is still severely limited.[75] In an eight-week ADF study, fasting showed a 6.8% decrease in blood glucose concentration and a 22.6% decrease in insulin concentration. [60] TRF also reduces insulin and glucose levels after a period of fasting, [7] and increases insulin sensitivity and β-cell reactivity. The beneficial effect of fasting is noticeable even despite the lack of weight loss. [74] Both ADF and TRF have been shown to reduce the HOMA-IR index. [7] A study of patients with type II diabetes treated with metformin showed improvement in diabetic parameters related to weight loss. Postprandial hyperglycemia was also reduced, and morning glucose levels were normalized. [7]

**Neurological diseases**

- **Multiple sclerosis**

Intermittent fasting may have a beneficial effect on multiple sclerosis (MS). IF induces a positive immunological effect by changing T lymphocyte subsets and increasing the number of lactic acid bacteria in the intestines, which can be used in MS therapy. A positive effect of IF on the nervous system through circadian, metabolic and cellular mechanisms has also been proven. Possible immunological effects include, among others, the reduction of pro-inflammatory cytokines and the migration of immune cells. As in the ketogenic diet, ketones are produced during fasting, which potentially constitute an alternative source of energy for the brain. [26,76]

- **Dementia**

Research is ongoing into the effects of IF on aging and cognitive function. Based on animal studies, it is initially assumed that IF may delay aging. Reduced oxidative stress, preserved memory and better biomarking have been demonstrated. The resistance of neurons to injury is increased. [25]

**Psychiatric disorders**

- **Mood**

TRE has been shown to have a positive effect on mood - reducing feelings of depression, low mood and fatigue, and increasing energy. [27] During long-term fasting, the secretion and turnover of serotonin increases, which has a positive effect on mood and reduces sensitivity to pain. Regulation of pain perception is also related to neurogenesis and increased synaptic plasticity. Mood improvement is influenced by fasting-related increased secretion of endogenous opioids, such as β-endorphins. [58]

**Cancer and other diet induced changes**

- **Cancer**

The effect of IF on cancer is not fully understood, however, it is suggested that in some patients fasting may reduce tumor growth and toxicity associated with chemotherapy. [76]

- **Hormone levels**

Fasting affects hormone levels. In addition to the previously mentioned decrease in insulin concentration, triiodothyronine is also decreased. This may be due to several mechanisms. First, fasting causes a reduction in TSH and TRH levels. Additionally, the activity of deiodinase III increases, which inactivates thyroid hormones. However, cortisol levels increase. Glucocorticoid hormone metabolism is also altered. Glucocorticoids cause anti-inflammatory reactions and hypertonicity of the cardiovascular system. Their secretion is under the control of diurnal rhythms. In humans, cortisol reaches acrophase at 7:00-8:00 am and gradually decreases until midnight. After IF, the diurnal rhythm of cortisol secretion changes, reaching its highest concentration later in the day. In addition, serum cortisol concentration increases after fasting. For other hormones, for example, growth hormone (GH), estradiol and melatonin, research is limited. Available studies have shown an increase in GH during fasting, a later acrophase of melatonin and an improvement in reproductive function (in a mouse model study). [77]

- **Liver diseases**

In a study of people with fatty liver disease, the use of ADF for 8-12 weeks contributed to a decrease in liver steatosis and fibrosis as well as a decrease in BMI and alanine aminotransferase. The possible etiology of positive changes in the liver is the peroxisome proliferator-activated receptor α activated during fasting, which promotes the degradation of nuclear receptor co-pressor 1 and liver autophagy allowing liver regeneration.[78]

- **Microbiome**

Intermittent fasting combined with increased relative protein consumption showed an effect on changing the composition of the microbiome. Microbes associated with the lean phenotype (C*hristensenella, Rikenellaceae, and Marvinbryantia*) were increased. *Christensenella* has a positive effect on regulating metabolic health, including glycemia and leptin levels. During the study, there was also an increase in circulating blood cytokines associated with weight loss and lipolysis- IL-4, IL-6, IL-8, and IL-13 indicating total body weight and fat loss.

Increases in IL-4 and IL-13 also negatively affected *Colidextribacter* and increased *Ruminoccus gauveaui*i group aboundance. [79]

Selected beneficial effects of intermittent fasting are summarized in the figure number 3.

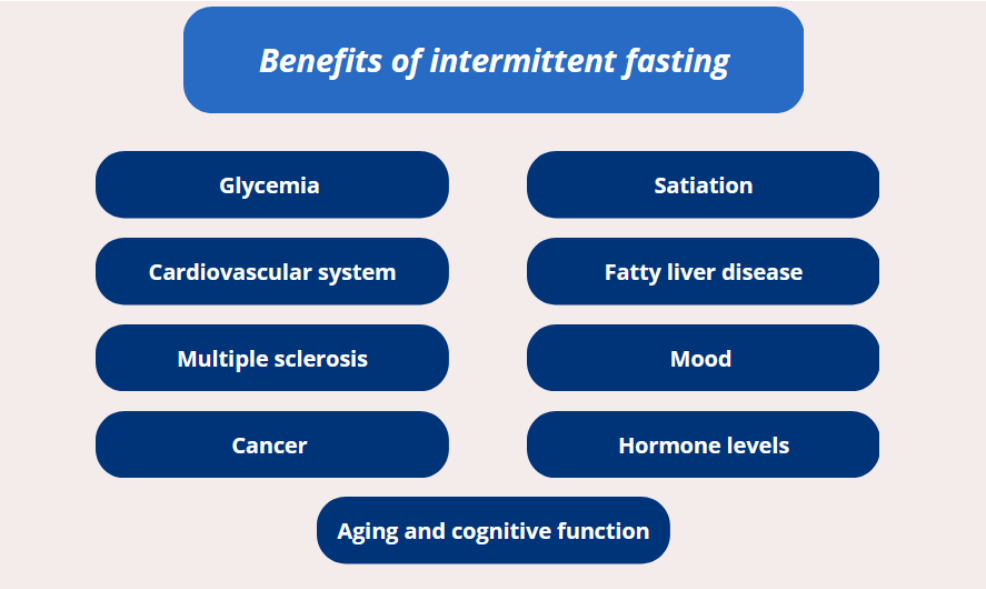


Figure 3. Selected beneficial effects of intermittent fasting. [6,34,39,42,43,46-48,50,57-62]

## 3. CONCLUSSIONS

Studies show that ketogenic diet and intermittent fasting have various positive effects such as anti-inflammatory activity, decrease in insulin secretion, antioxidant potential and neuroprotection. However, both IF and KD are not free from side effects. Side effects in KD include dehydration lethargy, halitosis or urolithiasis. Due to this it is not suitable for every patient, especially elderly, pregnant, patients with kidney failure or type 2 diabetes. In the case of intermittent fasting side effects include headaches, muscle pain, sleep disturbances, slight dizziness and negative emotions. The use of fasting is contraindicated in individuals with reactive hyperglycemia or taking antidiabetic drugs, pregnant or breastfeeding woman, children and people performing heavy physical work.

Both ketogenic diet and intermittent fasting have proven to be effective in weight reduction. In the case of IF the biggest impact on weight loss is calorie restriction, while in the case of the ketogenic diet, the potential impact is also attributed to increases in gluconeogenesis, metabolic state of nutritional ketosis and loss of free water through increased diuresis (loss of water weight rather than fat).

It is estimated that ketone bodies improve the metabolic state of the heart, because of the synthesis of the NO-producing enzyme - nitric oxide synthase, which promote vasodilation and increase blood flow through the heart muscle. Moreover, patients eliminate pro-inflammatory sugars from their diet. KD lower blood pressure due to weight loss, inhibits the sympathetic nervous system and increases diuresis. IF also shows positive effect on the cardiovascular system by anti-inflammatory processes and improvement of lipid and carbohydrate metabolism. Intermittent fasting reduces inflammatory markers, including C-reactive protein, Interleukin 6 and homocysteine.

The lipolysis of triglycerides in chylomicrons and the production of mature, spherical HDL cholesterol particles are increased. In the case of carbohydrate metabolism, the following are noticeable: decreased blood glucose concentration and insulin concentration, increased insulin sensitivity and β-cell reactivity. In cancer treatment ketone bodies in KD deprive cancer cells of their main source of energy – glucose and have anti-angiogenic activity, which limit tumor growth. Some cancers are unable to metabolize ketone bodies due to mitochondrial dysfunction and decreased enzyme activity. The use of fasting in cancer is much less understood and requires more research to demonstrate appropriate conclusions. Findings suggest that KD combines anticonvulsant and disease-modifying effects in drug-resistant epilepsy. Ketones may be a more efficient source of energy for the brain than glucose, they increase the number of mitochondria in cells, which causes the stabilization of the resting potential of neurons and their hyperpolarization. KD may be used also in the treatment of mood disorders and migraine, because it may affect neurotransmitters such as dopamine, serotonin, norepinephrine and has the anti-inflammatory effect. In the case of intermittent fasting the secretion and turnover of serotonin increases, also secretion of endogenous opioids, such as β-endorphins is increased. It not only has the effect of improving mood, but also, together with neurogenesis and increased synaptic plasticity, reduces the perception of pain.

The positive potential of ketogenic diet is also shown in neurodegenerative disorders such as Parkinson's disease, multiple sclerosis and dementia, because of neuroprotective effects. When it comes to fasting oxidative stress reduction, increased resistance of neurons to injury, preserved memory and better biomarking have been demonstrated. IF may also delay aging.

In summary the results of the current review indicate that there is no single best strategy for weight management. Both ketogenic diet and intermittent fasting can lead to clinically significant weight loss and improved metabolic indices. Strategies should be individualized based on health, comorbidities and preferences of the patients. Ketogenic diet can have positive impact on cardiovascular diseases, cancer, epilepsy resistant to treatment, mood disorders, migraine, dementia, Parkinson's disease, multiple sclerosis, and microbiome. In the case of intermittent fasting, the beneficial effect is on cardiovascular diseases, glycemia, satiation, fatty liver disease, mood disorders, aging and cognitive function, hormone levels, multiple sclerosis and potentially cancer. Future research should focus on the use of intermittent fasting and the ketogenic diet as adjuvant therapy for type 2 diabetes, cardiovascular disease and many more.

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**References**
[1] Ruze R, Liu T, Zou X, Song J, Chen Y, Xu R, et al. Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. Front Endocrinol (Lausanne) 2023;14. https://doi.org/10.3389/FENDO.2023.1161521.
[2] Tutor AW, Lavie CJ, Kachur S, Milani R V., Ventura HO. Updates on obesity and the obesity paradox in cardiovascular diseases. Prog Cardiovasc Dis 2023;78:2–10. https://doi.org/10.1016/J.PCAD.2022.11.013.
[3] Nussbaumerova B, Rosolova H. Obesity and Dyslipidemia. Curr Atheroscler Rep 2023;25:947–55. https://doi.org/10.1007/S11883-023-01167-2.
[4] Muscogiuri G, Barrea L, Laudisio D, Pugliese G, Salzano C, Savastano S, et al. The management of very low-calorie ketogenic diet in obesity outpatient clinic: a practical guide. J Transl Med 2019;17. https://doi.org/10.1186/S12967-019-2104-Z.
[5] McGaugh E, Barthel B. A Review of Ketogenic Diet and Lifestyle. Mo Med 2022;119:84.

[6] Varady KA, Cienfuegos S, Ezpeleta M, Gabel K. Clinical application of intermittent fasting for weight loss: progress and future directions. Nat Rev Endocrinol 2022;18:309–21. https://doi.org/10.1038/S41574-022-00638-X.

[7] Nowosad K, Sujka M. Effect of Various Types of Intermittent Fasting (IF) on Weight Loss and Improvement of Diabetic Parameters in Human. Curr Nutr Rep 2021;10:146–54. https://doi.org/10.1007/S13668-021-00353-5.

[8] Liu J, Yi P, Liu F. The Effect of Early Time-Restricted Eating vs Later Time-Restricted Eating on Weight Loss and Metabolic Health. J Clin Endocrinol Metab 2023;108:1824–34. https://doi.org/10.1210/CLINEM/DGAD036.

[9] Varady KA, Cienfuegos S, Ezpeleta M, Gabel K. Cardiometabolic Benefits of Intermittent Fasting. Annu Rev Nutr 2021;41:333–61. https://doi.org/10.1146/ANNUREV-NUTR-052020-041327.

[10] Arbour MW, Stec M, Walker KC, Wika JC. Clinical Implications for Women of a Low-Carbohydrate or Ketogenic Diet With Intermittent Fasting. Nurs Womens Health 2021;25:139–51. https://doi.org/10.1016/J.NWH.2021.01.009.

[11] Basolo A, Magno S, Santini F, Ceccarini G. Ketogenic Diet and Weight Loss: Is There an Effect on Energy Expenditure? Nutrients 2022;14. https://doi.org/10.3390/NU14091814.

[12] Masood W, Annamaraju P, Suheb MZK, Uppaluri KR. Ketogenic Diet. StatPearls 2023.

[13] Rusek M, Pluta R, Ułamek-Kozioł M, Czuczwar SJ. Ketogenic Diet in Alzheimer's Disease. Int J Mol Sci 2019;20. https://doi.org/10.3390/IJMS20163892.

[14] Ramesh R, Kanagasingam A, Sabrina S, Anushanth U. Starvation Ketoacidosis in a Young Healthy Female After Prolonged Religious Fasting. Cureus 2023;15. https://doi.org/10.7759/CUREUS.39962.

[15] Baumeister A, Gardemann J, Fobker M, Spiegler V, Fischer T. Short-Term Influence of Caffeine and Medium-Chain Triglycerides on Ketogenesis: A Controlled Double-Blind Intervention Study. J Nutr Metab 2021;2021. https://doi.org/10.1155/2021/1861567.

[16] Jamshed H, Beyl RA, Manna DLD, Yang ES, Ravussin E, Peterson CM. Early Time-Restricted Feeding Improves 24-Hour Glucose Levels and Affects Markers of the Circadian Clock, Aging, and Autophagy in Humans. Nutrients 2019;11. https://doi.org/10.3390/NU11061234.

[17] Choi A, Hallett M, Ehrlich D. Nutritional Ketosis in Parkinson's Disease — a Review of Remaining Questions and Insights. Neurotherapeutics 2021;18:1637. https://doi.org/10.1007/S13311-021-01067-W.

[18] Elortegui Pascual P, Rolands MR, Eldridge AL, Kassis A, Mainardi F, Kim-Anne L, et al. A meta-analysis comparing the effectiveness of alternate day fasting, the 5:2 diet, and time-restricted eating for weight loss. Obesity (Silver Spring) 2023;31 Suppl 1:9–21. https://doi.org/10.1002/OBY.23568.

[19] Patikorn C, Saidoung P, Pham T, Phisalprapa P, Lee YY, Varady KA, et al. Effects of ketogenic diet on health outcomes: an umbrella review of meta-analyses of randomized clinical trials. BMC Med 2023;21:1–12. https://doi.org/10.1186/S12916-023-02874-Y/FIGURES/2.

[20] Mohammadifard N, Haghighatdoost F, Rahimlou M, Rodrigues APS, Gaskarei MK, Okhovat P, et al. The Effect of Ketogenic Diet on Shared Risk Factors of Cardiovascular Disease and Cancer. Nutrients 2022;14. https://doi.org/10.3390/NU14173499.

[21] Arciero PJ, Poe M, Mohr AE, Ives SJ, Arciero A, Sweazea KL, et al. Intermittent fasting and protein pacing are superior to caloric restriction for weight and visceral fat loss. Obesity (Silver Spring) 2023;31 Suppl 1:139–49. https://doi.org/10.1002/OBY.23660.

[22] Weber DD, Aminzadeh-Gohari S, Tulipan J, Catalano L, Feichtinger RG, Kofler B. Ketogenic diet in the treatment of cancer - Where do we stand? Mol Metab 2020;33:102–21. https://doi.org/10.1016/J.MOLMET.2019.06.026.

[23] Norwitz NG, Sethi S, Palmer CM. Ketogenic diet as a metabolic treatment for mental illness. Curr Opin Endocrinol Diabetes Obes 2020;27:269–74. https://doi.org/10.1097/MED.0000000000000564.

[24] Brietzke E, Mansur RB, Subramaniapillai M, Balanza-Martínez V, Vinberg M, González-Pinto A, et al. Ketogenic diet as a metabolic therapy for mood disorders: Evidence and developments. Neurosci Biobehav Rev 2018;94:11–6. https://doi.org/10.1016/J.NEUBIOREV.2018.07.020.

[25] Stockman MC, Thomas D, Burke J, Apovian CM. Intermittent Fasting: Is the Wait Worth the Weight? Curr Obes Rep 2018;7:172–85. https://doi.org/10.1007/S13679-018-0308-9.

[26] Morales-Suarez-varela M, Sánchez EC, Peraita-Costa I, Llopis-Morales A, Soriano JM. Intermittent Fasting and the Possible Benefits in Obesity, Diabetes, and Multiple Sclerosis: A Systematic Review of Randomized Clinical Trials. Nutrients 2021;13. https://doi.org/10.3390/NU13093179.

[27] Jamshed H, Steger FL, Bryan DR, Richman JS, Warriner AH, Hanick CJ, et al. Effectiveness of Early Time-Restricted Eating for Weight Loss, Fat Loss, and Cardiometabolic Health in Adults With Obesity: A Randomized Clinical Trial. JAMA Intern Med 2022;182:953–62. https://doi.org/10.1001/JAMAINTERNMED.2022.3050.

[28] Watanabe M, Tuccinardi D, Ernesti I, Basciani S, Mariani S, Genco A, et al. Scientific evidence underlying contraindications to the ketogenic diet: An update. Obes Rev 2020;21. https://doi.org/10.1111/OBR.13053.

[29] Dowis K, Banga S. The Potential Health Benefits of the Ketogenic Diet: A Narrative Review. Nutrients 2021;13. https://doi.org/10.3390/NU13051654.

[30] Zarnowska IM. Therapeutic Use of the Ketogenic Diet in Refractory Epilepsy: What We Know and What Still Needs to Be Learned. Nutrients 2020;12:1–23. https://doi.org/10.3390/NU12092616.

[31] Corsello A, Trovato CM, Di Profio E, Cardile S, Campoy C, Zuccotti G, et al. Ketogenic diet in children and adolescents: The effects on growth and nutritional status. Pharmacol Res 2023;191. https://doi.org/10.1016/J.PHRS.2023.106780.

[32] Dressler A, Trimmel-Schwahofer P. The ketogenic diet for infants: How long can you go? Epilepsy Res 2020;164. https://doi.org/10.1016/J.EPLEPSYRES.2020.106339.

[33] Barry D, Ellul S, Watters L, Lee D, Haluska R, White R. The ketogenic diet in disease and development. Int J Dev Neurosci 2018;68:53–8. https://doi.org/10.1016/J.IJDEVNEU.2018.04.005.

[34] Saris CGJ, Timmers S. Ketogenic diets and Ketone suplementation: A strategy for therapeutic intervention. Front Nutr 2022;9. https://doi.org/10.3389/FNUT.2022.947567.
[35] Roekenes J, Martins C. Ketogenic diets and appetite regulation. Curr Opin Clin Nutr Metab Care 2021;24:359–63. https://doi.org/10.1097/MCO.0000000000000760.
[36] Horner K, Hopkins M, Finlayson G, Gibbons C, Brennan L. Biomarkers of appetite: is there a potential role for metabolomics? Nutr Res Rev 2020;33:271–86. https://doi.org/10.1017/S0954422420000062.
[37] Sukkar SG, Muscaritoli M. A Clinical Perspective of Low Carbohydrate Ketogenic Diets: A Narrative Review. Front Nutr 2021;8:642628. https://doi.org/10.3389/FNUT.2021.642628.
[38] Batch JT, Lamsal SP, Adkins M, Sultan S, Ramirez MN. Advantages and Disadvantages of the Ketogenic Diet: A Review Article. Cureus 2020;12. https://doi.org/10.7759/CUREUS.9639.
[39] Murugan M, Boison D. Ketogenic diet, neuroprotection, and antiepileptogenesis. Epilepsy Res 2020;167. https://doi.org/10.1016/J.EPLEPSYRES.2020.106444.
[40] Ko A, Kwon HE, Kim HD. Updates on the ketogenic diet therapy for pediatric epilepsy. Biomed J 2022;45:19–26. https://doi.org/10.1016/J.BJ.2021.11.003.
[41] McDonald TJW, Cervenka MC. Ketogenic Diet Therapies for Seizures and Status Epilepticus. Semin Neurol 2020;40:719–29. https://doi.org/10.1055/S-0040-1719077.
[42] Fila M, Chojnacki J, Pawlowska E, Sobczuk P, Chojnacki C, Blasiak J. The Ketogenic Diet in the Prevention of Migraines in the Elderly. Nutrients 2023;15. https://doi.org/10.3390/NU15234998.
[43] Barbanti P, Fofi L, Aurilia C, Egeo G, Caprio M. Ketogenic diet in migraine: rationale, findings and perspectives. Neurol Sci 2017;38:111–5. https://doi.org/10.1007/S10072-017-2889-6.
[44] Hayes MT. Parkinson's Disease and Parkinsonism. Am J Med 2019;132:802–7. https://doi.org/10.1016/J.AMJMED.2019.03.001.
[45] Dyńka D, Kowalcze K, Paziewska A. The Role of Ketogenic Diet in the Treatment of Neurological Diseases. Nutrients 2022;14. https://doi.org/10.3390/NU14235003.
[46] Bahr LS, Bock M, Liebscher D, Bellmann-Strobl J, Franz L, Prüß A, et al. Ketogenic diet and fasting diet as Nutritional Approaches in Multiple Sclerosis (NAMS): protocol of a randomized controlled study. Trials 2020;21. https://doi.org/10.1186/S13063-019-3928-9.
[47] Brockhoff JD, Bereswill S, Heimesaat MM. The impact of ketogenic diet on the onset and progression of multiple sclerosis. Eur J Microbiol Immunol (Bp) 2023;13:29–36. https://doi.org/10.1556/1886.2023.00020.
[48] Phillips MCL, Deprez LM, Mortimer GMN, Murtagh DKJ, McCoy S, Mylchreest R, et al. Randomized crossover trial of a modified ketogenic diet in Alzheimer's disease. Alzheimers Res Ther 2021;13. https://doi.org/10.1186/S13195-021-00783-X.
[49] Tao Y, Leng SX, Zhang H. Ketogenic Diet: An Effective Treatment Approach for Neurodegenerative Diseases. Curr Neuropharmacol 2022;20:2303–19. https://doi.org/10.2174/1570159X20666220830102628.

[50] Davis JJ, Fournakis N, Ellison J. Ketogenic Diet for the Treatment and Prevention of Dementia: A Review. J Geriatr Psychiatry Neurol 2021;34:3–10. https://doi.org/10.1177/0891988720901785.
[51] Weber DD, Aminazdeh-Gohari S, Kofler B. Ketogenic diet in cancer therapy. Aging 2018;10:164–5. https://doi.org/10.18632/AGING.101382.
[52] Barrea L, Caprio M, Tuccinardi D, Moriconi E, Di Renzo L, Muscogiuri G, et al. Could ketogenic diet "starve" cancer? Emerging evidence. Crit Rev Food Sci Nutr 2022;62:1800–21. https://doi.org/10.1080/10408398.2020.1847030.
[53] Adak A, Khan MR. An insight into gut microbiota and its functionalities. Cell Mol Life Sci 2019;76:473–93. https://doi.org/10.1007/S00018-018-2943-4.
[54] Paoli A, Mancin L, Bianco A, Thomas E, Mota JF, Piccini F. Ketogenic Diet and Microbiota: Friends or Enemies? Genes (Basel) 2019;10. https://doi.org/10.3390/GENES10070534.
[55] Mengoli M, Conti G, Fabbrini M, Candela M, Brigidi P, Turroni S, et al. Microbiota-gut-brain axis and ketogenic diet: how close are we to tackling epilepsy? Microbiome Research Reports 2023;2. https://doi.org/10.20517/MRR.2023.24.
[56] Santos HO, Macedo RCO. Impact of intermittent fasting on the lipid profile: Assessment associated with diet and weight loss. Clin Nutr ESPEN 2018;24:14–21. https://doi.org/10.1016/J.CLNESP.2018.01.002.
[57] Fanti M, Mishra A, Longo VD, Brandhorst S. Time-Restricted Eating, Intermittent Fasting, and Fasting-Mimicking Diets in Weight Loss. Curr Obes Rep 2021;10:70–80. https://doi.org/10.1007/S13679-021-00424-2.
[58] Wang Y, Wu R. The Effect of Fasting on Human Metabolism and Psychological Health. Dis Markers 2022;2022. https://doi.org/10.1155/2022/5653739.
[59] Malinowski B, Zalewska K, Węsierska A, Sokołowska MM, Socha M, Liczner G, et al. Intermittent Fasting in Cardiovascular Disorders-An Overview. Nutrients 2019;11. https://doi.org/10.3390/NU11030673.
[60] Zhang Q, Zhang C, Wang H, Ma Z, Liu D, Guan X, et al. Intermittent Fasting versus Continuous Calorie Restriction: Which Is Better for Weight Loss? Nutrients 2022;14. https://doi.org/10.3390/NU14091781.
[61] Poggiogalle E, Jamshed H, Peterson CM. Circadian regulation of glucose, lipid, and energy metabolism in humans. Metabolism 2018;84:11–27. https://doi.org/10.1016/J.METABOL.2017.11.017.
[62] Chair SY, Cai H, Cao X, Qin Y, Cheng HY, Timothy MNG. Intermittent Fasting in Weight Loss and Cardiometabolic Risk Reduction: A Randomized Controlled Trial. J Nurs Res 2022;30:E185. https://doi.org/10.1097/JNR.0000000000000469.
[63] Sundfør TM, Svendsen M, Tonstad S. Effect of intermittent versus continuous energy restriction on weight loss, maintenance and cardiometabolic risk: A randomized 1-year trial. Nutr Metab Cardiovasc Dis 2018;28:698–706. https://doi.org/10.1016/J.NUMECD.2018.03.009.
[64] Jospe MR, Roy M, Brown RC, Haszard JJ, Meredith-Jones K, Fangupo LJ, et al. Intermittent fasting, Paleolithic, or Mediterranean diets in the real world: exploratory secondary analyses of a weight-loss trial that included choice of diet and exercise. Am J Clin Nutr 2020;111:503–14. https://doi.org/10.1093/AJCN/NQZ330.

[65] Welton S, Minty R, O'Driscoll T, Willms H, Poirier D, Madden S, et al. Intermittent fasting and weight loss: Systematic review. Canadian Family Physician 2020;66:117.
[66] Pérez-Gerdel T, Camargo M, Alvarado M, Ramírez JD. Impact of Intermittent Fasting on the Gut Microbiota: A Systematic Review. Adv Biol 2023;7. https://doi.org/10.1002/ADBI.202200337.
[67] Stanislawski MA, Frank DN, Borengasser SJ, Ostendorf DM, Ir D, Jambal P, et al. The Gut Microbiota during a Behavioral Weight Loss Intervention. Nutrients 2021;13. https://doi.org/10.3390/NU13093248.
[68] Templeman I, Smith HA, Chowdhury E, Chen YC, Carroll H, Johnson-Bonson D, et al. A randomized controlled trial to isolate the effects of fasting and energy restriction on weight loss and metabolic health in lean adults. Sci Transl Med 2021;13. https://doi.org/10.1126/SCITRANSLMED.ABD8034.
[69] Thomas EA, Zaman A, Sloggett KJ, Steinke S, Grau L, Catenacci VA, et al. Early time-restricted eating compared with daily caloric restriction: A randomized trial in adults with obesity. Obesity (Silver Spring) 2022;30:1027–38. https://doi.org/10.1002/OBY.23420.
[70] Kim BH, Joo Y, Kim MS, Choe HK, Tong Q, Kwon O. Effects of Intermittent Fasting on the Circulating Levels and Circadian Rhythms of Hormones. Endocrinol Metab (Seoul) 2021;36:745–56. https://doi.org/10.3803/ENM.2021.405.
[71] Poggiogalle E, Jamshed H, Peterson CM. Circadian regulation of glucose, lipid, and energy metabolism in humans. Metabolism 2018;84:11–27. https://doi.org/10.1016/J.METABOL.2017.11.017.
[72] Freire R. Scientific evidence of diets for weight loss: Different macronutrient composition, intermittent fasting, and popular diets. Nutrition 2020;69. https://doi.org/10.1016/J.NUT.2019.07.001.
[73] Arciero PJ, Arciero KM, Poe M, Mohr AE, Ives SJ, Arciero A, et al. Intermittent fasting two days versus one day per week, matched for total energy intake and expenditure, increases weight loss in overweight/obese men and women. Nutr J 2022;21. https://doi.org/10.1186/S12937-022-00790-0.
[74] Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. Cell Metab 2018;27:1212-1221.e3. https://doi.org/10.1016/J.CMET.2018.04.010.
[75] Varady KA, Runchey MC, Reutrakul S, Vidmar AP, Chow LS. Clinical potential of fasting in type 1 diabetes. Trends Endocrinol Metab 2024;35:413–24. https://doi.org/10.1016/J.TEM.2024.01.007.
[76] He Z, Xu H, Li C, Yang H, Mao Y. Intermittent fasting and immunomodulatory effects: A systematic review. Front Nutr 2023;10. https://doi.org/10.3389/FNUT.2023.1048230.
[77] Kim BH, Joo Y, Kim MS, Choe HK, Tong Q, Kwon O. Effects of Intermittent Fasting on the Circulating Levels and Circadian Rhythms of Hormones. Endocrinol Metab (Seoul) 2021;36:745–56. https://doi.org/10.3803/ENM.2021.405.

[78] Patikorn C, Roubal K, Veettil SK, Chandran V, Pham T, Lee YY, et al. Intermittent Fasting and Obesity-Related Health Outcomes: An Umbrella Review of Meta-analyses of Randomized Clinical Trials. JAMA Netw Open 2021;4. https://doi.org/10.1001/JAMANETWORKOPEN.2021.39558.

[79] Mohr AE, Sweazea KL, Bowes DA, Jasbi P, Whisner CM, Sears DD, et al. Gut microbiome remodeling and metabolomic profile improves in response to protein pacing with intermittent fasting versus continuous caloric restriction. Nat Commun 2024;15. https://doi.org/10.1038/S41467-024-48355-5.