ejpmr, 2024, 11(3), 283-292

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

WEIGHT LOSS DIET STRATEGY IN AMELIORATING OBESITY: KETOGENIC DIET AND INTERMITTENT FASTING

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Article Received on 17/01/2024 **Article Revised on 07/02/2024** **Article Accepted on 27/02/2024**

ABSTRACT

Obesity is considered as one of the major global health concerns due to its significant increase in prevalence post COVID-19 pandemic. To combat obesity, several strategies were tried to minimise the use of marketed allopathic weight loss drugs among which dietary strategy is one of them. The ketogenic diet and intermittent fasting were the most well-known and extensively utilised weight loss plan. Ketogenic diet is composed mostly with fat and relatively lower carbohydrates. Intermittent fasting (IF) refers to the frequent periods of very limited or no calorie intake, which includes periods of intentional withdrawal from food and water consumption. Recently, intermittent fasting is gaining popularity and is consciously suggested as a potential therapeutic adjuvant. Few clinical research studies revealed the safety and pharmacological profile of ketogenic diet and intermittent fasting in promoting weight loss. In contrast, till now there are limited research studies on weight loss management post discontinuation of diet, which is more challenging now-a-days. Hence, the current review mainly attempted to address the mechanism by which the ketogenic diet and intermittent fasting produces weight loss and ameliorates obesity and associated metabolic disorders. However, it is necessary to continue research involving the consumption of ketogenic diet during intermittent fasting for its prolonged weight loss in obesity and associated metabolic disorders.

KEYWORDS: Ketogenic diet, Intermittent fasting, low Carbohydrates and Metabolic disorders.

INTRODUCTION

Obesity is one of the most important global public health concerns nowadays, which is linked to type 2 diabetes mellitus (T2DM), cardiovascular disorders, osteoarthritis, obstructive sleep apnea, depression, and cancer.[1] Over 1.9 billion adults over the age of 18 were classified as overweight in 2016, with over 650 million of those individuals being obese, according to the World Health Organisation (WHO).[2] The ICMR-INDIAB study indicates that between 11.8% and 31.3% and 16.9% and 36.3% of Indians are obese.[3] Obesity is a complex illness with several contributing factors. The most worrying one is excessive calorie intake, which is primarily brought on by adopting bad western diets that emphasise overindulging in highly processed, high-fat, high-carbohydrate, and low-fiber foods. Energy imbalance and fat deposition result from a diet high in calories combined with little activity. Thus, managing and losing weight is one of the primary goals of treating obesity and overweight patients. Reducing calories is the first step in every weight-loss plan. In order to reduce weight, those who are overweight or obese should also engage in aerobic and strength training exercises together with a low-calorie diet.[4] Dietary adjustments remain the most important aspect in weight-management strategies. Weight-management approaches should consider the amount of food consumed, the type of food consumed, and meal scheduling. Diet options for weight loss and control include a low-fat diet, a low-carbohydrate diet, a ketogenic diet (Extremely low carbohydrate diet), a high-protein diet, and the Mediterranean diet. Intermittent fasting and meal timing are two weight loss strategies that modify the timing of meal consumption.[5]

The ketogenic diet, also known as a very low carbohydrate diet, is a fasting-like diet that has a minimal carbohydrate content (<20 g/day), 1-1.5 g protein/Kg ideal body weight, 15–30 g fat/day, and 500–800 calories intake/daily. The ketogenic diet includes quick weight reduction, satiety induction, and muscle mass preservation, all of which result in its greater compliance. Therefore, the ketogenic diet is now suggested as an effective and realistic dietary strategy in obese individuals.[6] Intermittent fasting (IF) refers to frequent periods of very limited or no caloric intake, which includes periods of intentional withdrawal from food and drink consumption to attain calorie consumption from 0 to 25% of usual caloric demands. It

typically consists of a 16-hour fast every day, a 24-hour fast on alternate days, or a two-day fast once a week. On non-fasting days, consumption can be at-will, limited to a predetermined food composition, or reserved to meet a certain calorie intake of up to 125% of usual caloric demands.[7] Intermittent fasting is currently one of the most popular methods for controlling calorie intake, leading to weight loss and improved health and lifestyle. In this review, we will discuss in detail the benefits and drawbacks of the ketogenic diet strategy and the intermittent fasting timing of meal strategy in management of weight loss, which can potentially lessen obesity to some extent.

Ketogenic diet

Protocol of ketogenic diet

Initially the ketogenic diet was used as a successful therapy for epilepsy in children who had not responded to medicines in 1920.[8] A Ketogenic diet contains a mixture of 20-25% of protein, 5-10% of carbohydrates and 70-80% of fat that constitutes about 100% of the meal. The composition of the diet was tabulated in table-1.[9]

Table 1: Protocol of ketogenic diet.

Protein (20-25%)	**Carbohydrates (Low carb) (5-10%)**	**Fat (70-80%)**
Meat Ground beef, pork chops, beef, lamb, chicken,duck	Broccoli Cabbage Cauliflower Celery Cucumber Fennel Green beans Mushrooms Okra Onions Peppers Pumpkin Radishes Spinach Sprouts Tomatoes Turnips	**Oils from Nuts** Coconut, olive, avocado, sesame, hazelnut, walnut, almond
Deli meats Hotdogs, sausage,pepperoni		**Non- dairy fats** Lard, ghee, duck-fat, coconut cream
Canned meats Tuna, salmon, chicken, crab		**Dairy fats** Butter, cream, sour cream, heavy cream, cream cheese, yogurt
Organ meat Liver, heart, tripe		**Full-fat salad dressings** Ranch, blue cheese, Italian
Fish Salmon, cod, tuna		**Full-fat cheeses** Cheddar, mozzarella, Swissblue
Seafood crab, mussels, octopus, oysters		**Sauces** Hollandaise, mayonnaise, aioli
Plant- based protein Tofu, black soybeans		**Other** Nuts, seeds, avocado's, olives

Ketogenic diet versions

There are various versions of the ketogenic diet, but in this review, we focussed mainly on a few of them based on the available scientific literature. Some variations of the ketogenic diet include the conventional ketogenic diet, the modified Atkins diet, the very low energy ketogenic diet, and the ketogenic Mediterranean diet.

Classic ketogenic diet

Historically, the standard ketogenic diet has been used for a variety of epileptic patients. The typical therapeutic ketogenic diet consists of 90% fat, 6% protein, and 4% carbohydrates, resulting in a 4:1 fat-to-carbohydrate plus-protein ratio.[10]

Modified Atkins diet

In 2003, the modified Atkins diet took the place of the traditional ketogenic diet, limiting daily carbohydrate consumption to 10–20 gram. When it comes to protein and carbohydrate consumption, the modified Atkins diet has higher proportions than the traditional ketogenic diet. The modified Atkins diet is composed of 65% fat, 30% protein, and 5% carbohydrates.[11]

Very low energy ketogenic diet

The very low-energy ketogenic diet approximates 44% fat and 43% protein, with a daily energy intake of less than 800 kcal. This diet closely resembles fasting by limiting daily carbohydrate consumption to less than 30 g/day.[6]

Ketogenic mediterranean diet

The ketogenic Mediterranean diet is considered as a very low-carbohydrate diet (lower than 30 or 50 g/day).[12]

Ketogenic diet intervention

Eight weeks of a ketogenic diet consisting of five meals a day is recommended by a research by Natalia *et al*. Breakfast, snack, lunch, snack II, and supper were consumed throughout five meals. Researchers identified changes in body weight, inflammatory markers, and metabolic state over the 8-week intervention. Furthermore, an 8-week diet plan is commonly followed by women who are affected mainly by social media.[13]

Mechanisms of ketogenic diet

The ketogenic diet impacts several physiological and metabolic systems by causing physiological ketosis through decreased glucose, elevated fatty acid concentrations, and enhanced bio energetic reserves.

Reduced consumption of carbohydrates causes a rise in glucagon concentrations, which in turn causes a drop in insulin and leptin levels, as well as a reduction in lipogenesis and an increase in lipolysis.[14] In contrast, the fuel sources of a ketogenic diet consist of 10% glucose produced from gluconeogenesis, 20% ketone bodies derived from adipose reserves by lipolysis and ketogenesis, and 70% fatty acids derived from dietary fat and lipolysis of adipose tissue pools.[15] A ketogenic diet induces ketosis, which keeps the amounts of ketone bodies at healthy levels. Fig. 1 illustrates how the body switches to using just ketones for energy after a few days or weeks on the diet. This process is called "keto-adaptation" and might differ from person to person.[16] Although the exact processes of keto-adaptation are yet unknown, some researchers have hypothesised that mitochondrial biogenesis and the decrease of mitochondrial damage in oxidative organs, such the brain and muscle, may be among them.[17]

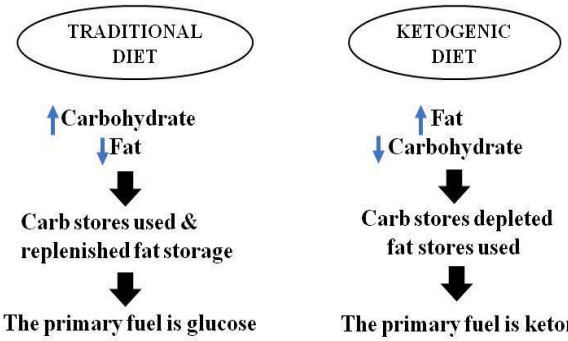

Fig. 1: Comparision of energy fuel source in traditional diet and ketogenic diet.

Mechanisms of a ketogenic diet on weight Loss and Obesity

The precise mechanisms behind weight loss remain unclear. A 12 week research study shows that low-carbohydrate diets lower insulin fluxes and boost lipolysis, resulting in improved fat breakdown.[18] Another potential weight reduction strategy is increasing the body's gluconeogenesis to provide glucose as a result of reduced carbohydrate consumption.[19] Direct appetite suppression is another hypothesised weight loss strategy. In a clinical research, intake of a low-carb, ketogenic diet showed significantly decreased appetite, prompting the authors to hypothesise that ketosis may suppress hunger.[20]

The carbohydrate-insulin hypothesis of obesity states that when people consume too much carbohydrate, their insulin levels rise. As a result, glucose and fatty acids are directed towards storage rather than utilisation, resulting in "internal starvation" defined by intense hunger, decreased energy expenditure, and increased weight gain.[21] The ketogenic diet induces a glucagon-dominant physiological state comparable to fasting, with a high glucagon-to-insulin ratio, and encourages glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis. The body transits from a glucocentric to a ketocentric condition, where energy is mostly acquired via beta-oxidation of dietary and endogenous fatty acids, as well as ketogenesis/ketolysis, as represented in fig. 2.[22] The efficacy of ketogenic diets in obesity and weight loss might be attributed to high fat mass reduction, preservation of resting energy expenditure and lean muscle mass, and an increased rate of fat oxidation. Marco Castellan *et al*. discovered that a very low calorie ketogenic diet is a viable option for significant weight loss in overweight and obese people. The findings were achieved early in the ketogenic phase and were stable for up to two years. As a result, researchers concluded that a very low-calorie ketogenic diet is a viable intervention as part of a multi-pronged strategy under medical supervision.[23]

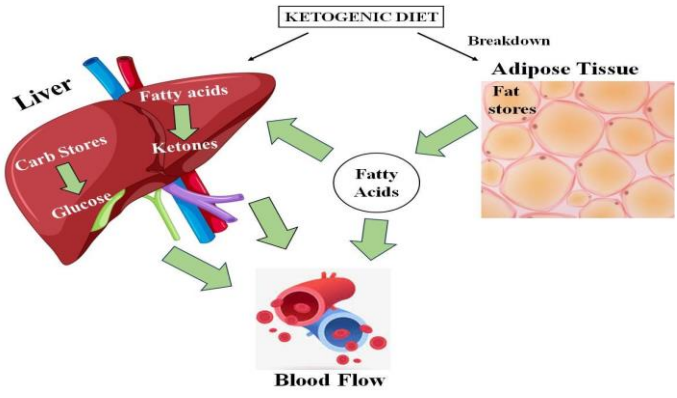

Fig. 2: Possible mechanism of ketogenic diet in weight loss.

PROS of ketogenic diet

Health benefits of consuming ketogenic diet was depicted in fig. 3 and includes.

Suppression of appetite

Consuming lower carbohydrates naturally lowers appetite. Consuming more fat and protein while limiting carbs leads to much reduced calorie consumption.[24]

Reduction of chance of developing some malignancies

Researchers hypothesised that when combined with radiation and chemotherapy, the ketogenic diet would be a suitable and safe adjuvant treatment. This is because it would expose cancer cells to higher oxidative stress levels than healthy cells, ultimately resulting in their death.[25]

Strengthening the heart

The ketogenic diet can lower blood pressure; raise high density lipid cholesterol levels, and lower triglycerides, reducing the risk of developing cardiovascular disease.[26]

Lessening seizures

Medical practitioners usually recommend a ketogenic diet to children who have epilepsy in an attempt to change the brain's "excitability" and perhaps reduce or even eliminate seizures.[27]

Management of Type 2 diabetes

Lower carbohydrate consumption is the most effective way to reduce insulin and blood sugar levels, which may help treat and even reverse type II diabetes.[28]

Alleviate PCOS symptoms

A high-carbohydrate diet may cause weight gain and skin problems in people with PCOS, among other unfavourable outcomes. PCOS symptoms can be reduced by following a ketogenic diet low in carbohydrates.[29]

Improves brain conditions

Ketones are produced on a ketogenic diet and have neuroprotective qualities that support and safeguard brain and nerve tissue. Therefore, a ketogenic diet may help control or prevent conditions like Alzheimer's disease.[30]

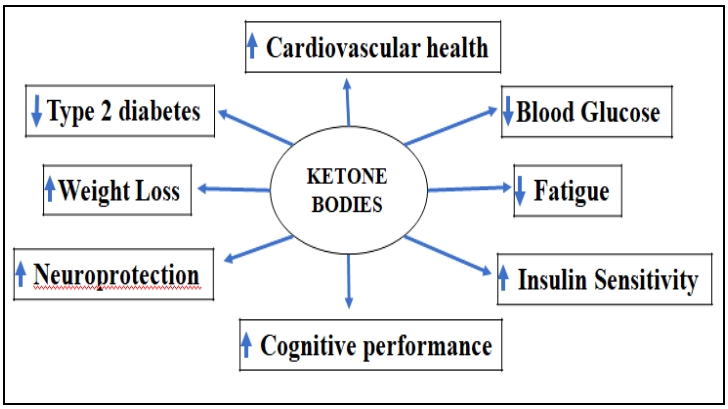

Fig. 3: Health benefits of ketogenic diet.

CONs of the ketogenic diet

Long-term ketogenic diets have been linked to increased risk of kidney stones, high blood uric acid, and osteoporosis from low calcium intake. The most common short-term negative effects include dehydration, keto flu, and vision impairment. Other short-term adverse effects include hyperuricemia, hypoglycemia, halitosis, lethargy, gastrointestinal problems, and diarrhoea.[31]

Contraindications of ketogenic diet

Individuals suffering with type 1 diabetes

Patients with type 1 diabetes are insulin dependent. Consumption of a ketogenic diet may create dangerously low blood sugar levels.

Individuals who have undergone gallbladder excision

Bile is stored in the gallbladder which aids in digestion of fat. On a high-fat diet, an individual will not feel their best without this organ.

Others

The ketogenic diet is also contraindicated in persons with pancreatitis, liver failure, lipid metabolism disorders, intrinsic carnitine deficit, carnitine palmitoyl transferase deficiency, carnitine translocase insufficiency, porphyrias or pyruvate kinase deficiency.[32]

Intermittent fasting

In recent years, intermittent fasting has emerged as one of the most popular weight loss programmes. Intermittent fasting is defined as alternating intervals of eating and not eating. Intermittent fasting participants are not needed to precisely monitor their daily calorie intake or avoid any specific food groups or macronutrients. These attributes contribute to greater acceptance.[33]

Protocol of intermittent fasting diet

The number of fast days and calorie limitations for various intermittent fasting techniques may vary. There are six different diet methods of intermittent fasting which were represented in fig. 4.[34]

The 5:2 fasting

The 5:2 fasting is characterized by consuming a diet normally for five days a week and reduction of daily caloric intake to 20% on the other two days.

The 14:10 fasting

The 14:10 fasting method is characterized by eating for ten hours and fasting for fourteen hours. According to a 2021 study published in Nutrition & Diabetes, people who combined a 14:10 diet with wholesome food and regular exercise really lost more weight.[35]

The 16:8 fasting

The 16:8 approach of intermittent fasting is characterized by limiting the daily eating window to eight hours and fasting for 16 hours.

Alternate-day fasting

Alternate day fasting is characterized by fasting every other day. This strategy comes in multiple flavours; some suggested consuming around 500 calories during the fasting days, while others advise you to eat almost nothing at all during fasting days.

Eat-Stop-Eat fasting

Eat stop eat fasting is characterized by consuming once or twice a week with a gap of 24-hour complete fast. Disadvantages of this method include fasting for a whole day without eating might be risky in some situations and shouldn't be done carelessly.

The warrior fasting

Warrior type fasting differs greatly from the others in that it emphasizes eating mostly at night. Fitness writer Ori Hofmekler is credited with creating the Warrior fasting strategy. It entails consuming fewer amounts of raw fruits and vegetables during the day and one large meal within a 4-hour eating window at night.

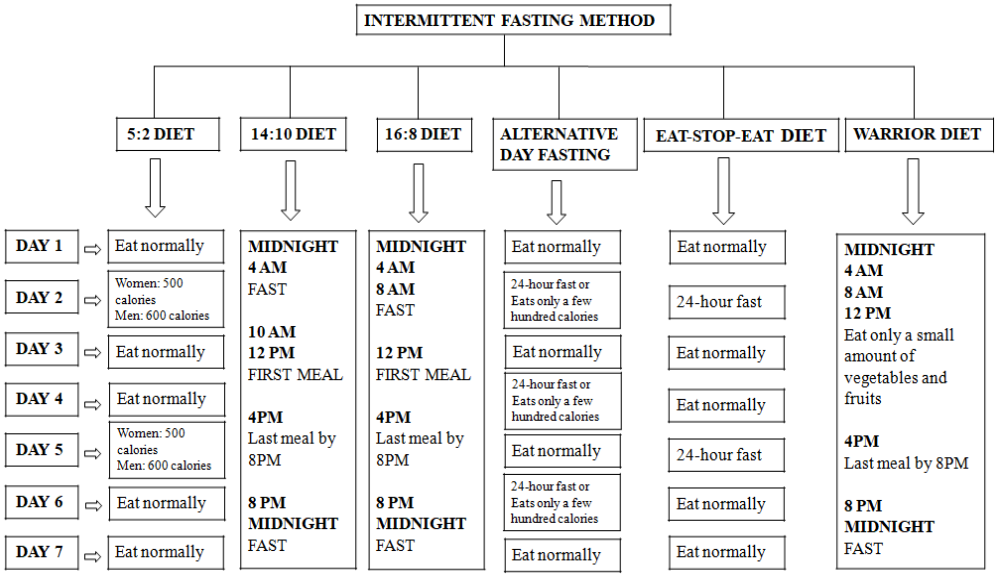

Fig. 4: Intermittent fasting methods.

Mechanisms of intermittent fasting

The thermic impact of food (TEF) is the increase in energy expenditure caused by meal consumption, which occurs over a period of 3-5 hours and ranges from 5-15%. TEF is mostly related to the energy rate at which nutrients are eaten, absorbed, and stored. Depending on the level of physical activity, twelve to twenty-four hours of fasting often results in a 20% decline in blood glucose and the depletion of hepatic glycogen. A change in the metabolic mode occurs after that, allowing for the utilisation of free fatty acids, fat-derived ketone bodies, and non-hepatic glucose as energy sources. Depending on their body weight and composition, the majority of individuals may last 30 or more days without eating if they have enough ketone bodies, free fatty acids, and proper gluconeogenesis.

Intermittent fasting affects brain neurochemistry and neural network activity via increasing brain function and peripheral energy consumption. The hippocampus, striatum, hypothalamus, and brainstem are four brain regions that play important roles in intermittent fasting adaption. Furthermore, the brain interacts with all peripheral organs involved in energy metabolism. Intermittent fasting stimulates parasympathetic activity in autonomic neurons responsible for gastrointestinal motility, heart rate, and blood pressure. Intermittent fasting also lowers body fat by depleting glycogen in liver cells and creating ketone bodies. Furthermore, it enhances insulin sensitivity in muscle and liver cells by inhibiting IGF-1 production. Intermittent fasting decreases oxidative damage and inflammation throughout the body and brain, as seen in fig. 5. Preclinical and clinical research revealed that introducing intermediate fasting into adult lifestyles, especially for

overweight and inactive adults, can improve health and reduce the risk of chronic illnesses.[36]

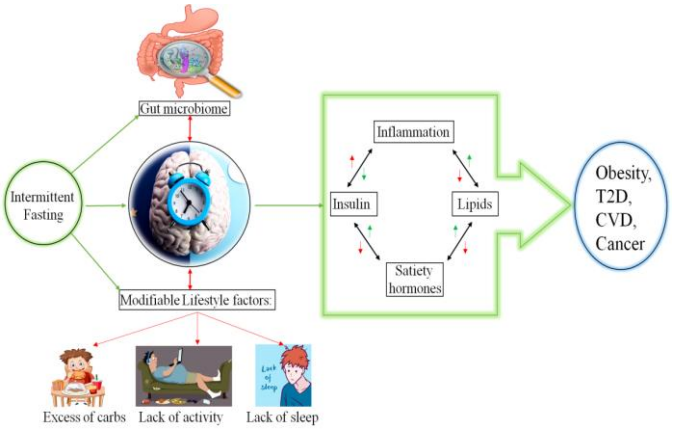

Fig. 5: Mechanisms of intermittent fasting.

Mechanisms of intermittent fasting on weight Loss and Obesity

Intermittent fasting is offered as a novel and promising technique to obesity treatment. Numerous clinical trials and a few preclinical research studies revealed that intermittent fasting (IF) has promise effects on obesity by avoiding weight gain and improving glucose homeostasis and metabolic function. IF can also reduce visceral fat, lessen the risk of cardiometabolic illness, and improve muscle function. Researchers discovered that changes in appetite and gut microbiome are the two most critical mechanisms by which intermittent fasting causes weight reduction.[37] A clinical investigation demonstrated that the combination of alternate day fasting and regular exercise can successfully drop weight and enhance cholesterol metabolism in overweight or obese patients.[38]

Intermittent fasting reduces plasma total triglycerides significantly via boosting triglyceride lipolysis in chylomicrons and HDL particle production. It also promotes weight reduction by increasing β-hydroxybutyrate and ketone levels, reducing oxidative stress, and decreasing hunger. Furthermore, IF affects the gut microbiome, facilitating the development and maintenance of beneficial microorganisms.[39] Alternate-day fasting can reduce blood glucose, leptin, TNF-α, and insulin growth factor-1 levels, leading to significant weight reduction in obese individuals.[40] According to few clinical research studies, intermittent fasting increases the expression of vascular endothelial growth factor (VEGF) in white adipose tissue (WAT), promotes angiogenesis, and polarizes macrophages in adipose tissues. These effects lead to adipocyte browning, improved insulin sensitivity, and successfully reduce obesity.[42]

PROS of intermittent fasting

Health benefits of intermittent fasting other than promoting weight loss and obesity were depicted in fig. 6.[42]

Type 2 Diabetes

During intermittent fasting, the liver employs two restriction enzymes, phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), to regenerate glucose and sustain blood glucose levels via enhanced gluconeogenesis.

Cancer

Intermittent fasting may have the ability to reduce chemotherapy induced side effects and increase the efficiency of chemotherapy and cancer-related adverse effects and enhance day-to-day functioning.

Neurological diseases

Intermittent fasting may effectively reduce histone deacetylase 1 (HDAC1) levels, which play a critical role in neuroprotection. Thus, intermittent fasting may have neuroprotective effects, particularly in Alzheimer's disease. In addition, intermittent fasting increases brain-derived neurotrophic factor (BDNF), which has promise benefits on depression and cognitive decline.

Aging

Intermittent fasting improves cognitive function and lowers oxidative stress in middle-aged persons. Additionally, it slows the progression of age-related brain degeneration.

Heart health

Intermittent fasting may have a protective effect from ischemia and enhance a variety of cardio metabolic effects.

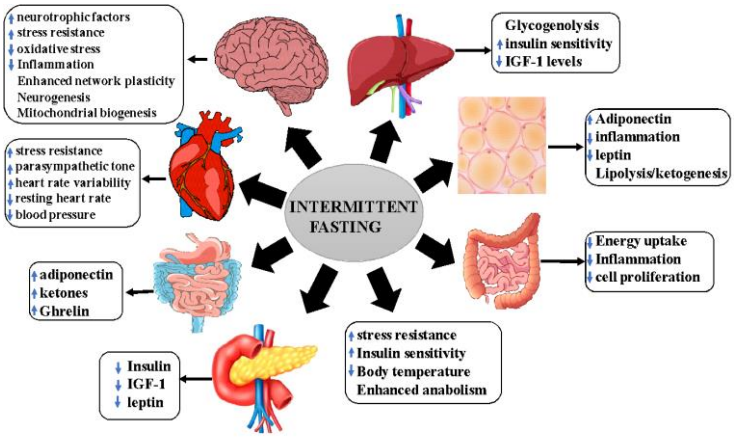

Fig. 6: Pharmacological mechanisms of intermittent fasting on overall health CONS of intermittent fasting.

Certain side effects may occur during the fasting phase of intermittent fasting, with dizziness, weakness, and hypoglycemia being the most typically reported. Intermittent fasting may have detrimental consequences for certain people. Individuals who fast may have headaches as their bodies adjust to consuming fewer calories. Bloating and heartburn are common digestive issues, but constipation, nausea, and diarrhoea are other possible adverse effects. Anaemia, hunger, irritability, disorientation, and dehydration are some of the other possible side effects. Few research studies found that fasting persons may develop dizziness, headaches, chills, poor breath, lack of focus, and sleeplessness.[43] Intermittent fasting can also lead to increased hunger and food cravings. Furthermore, IF indicated that fasting for 14 hours or longer may increase the chance of developing gallstones. It may also decrease immunity, rendering fasting persons more susceptible to diseases such as cancer. Excessive calorie restriction has been associated with hormonal dysregulation, which can affect men's testosterone levels and cause irregular menstrual cycles in women.[43]

Clinical conditions in which intermittent fasting is contraindicated

Individuals with hormonal abnormalities should avoid intermittent fasting. It is also not recommended for pregnant or breastfeeding women, persons with diabetes, eating problems, or those who are underweight. Furthermore, it is not recommended for children and teens, persons recuperating from surgery, and anyone with a history of eating problems.[43]

Ketogenic Diet vs. Intermittent Fasting

The fundamental variation between these diets may be found in their application and focus. The ketogenic diet focuses mostly on what foods to eat which includes a high-fat, low-carb diet in which fat is the primary source of energy. In contrast, meal time and fasting cycles are critical components of intermittent fasting. Fig. 7 and 8 depicted the benefits of the keto diet and intermittent fasting. Continuous intermittent fasting leads to the creation of ketones, which is the exact mechanism for a ketogenic diet, which acts as a recommendation for primary care practitioners (PCP) as a beneficial guide for patient management.[44]

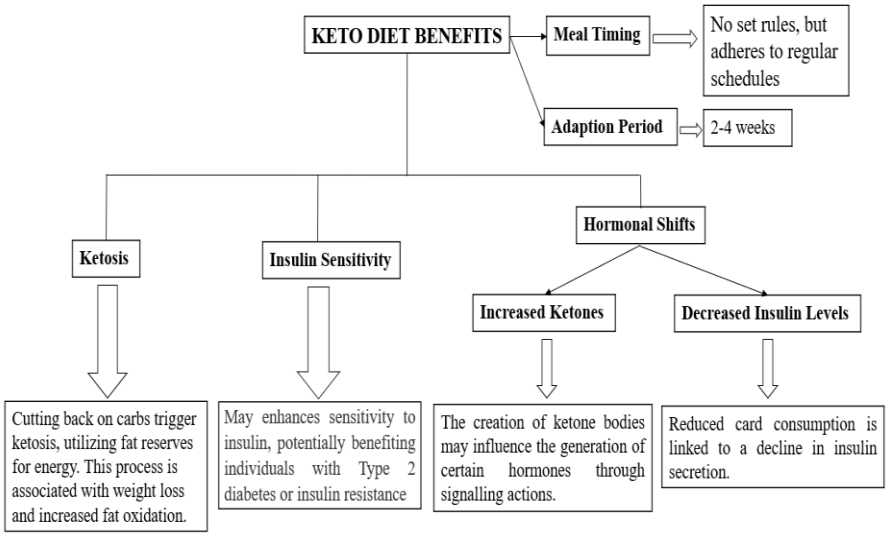

Fig. 7: Ketogenic diet benefits on overall health.

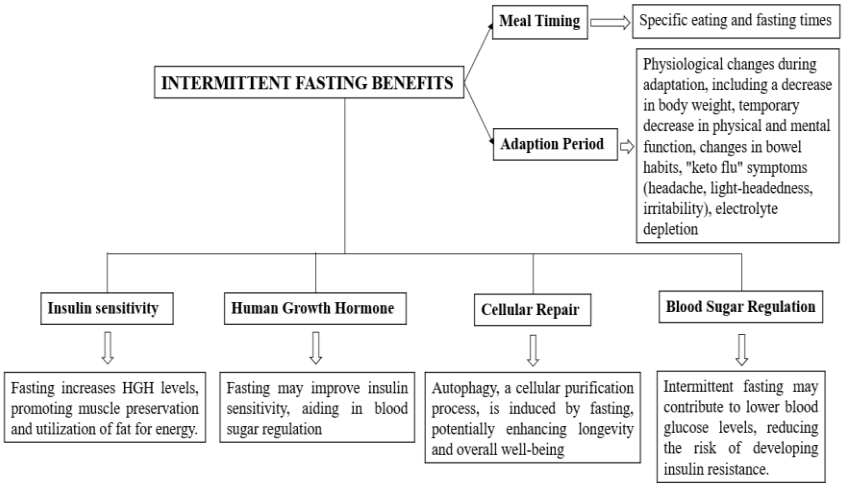

Fig. 8: Intermittent fasting benefits on overall health.

Conclusion and future insights

In summary, the ketogenic diet limits carbohydrate intake to less than 10% of total calories, which promotes ketosis and can result in fast weight reduction. Existing scientific evidence suggests that the ketogenic diet may assist to reduce obesity. The ketogenic diet is linked with minor adverse effects as well as long-term health hazards such as mineral vitamin insufficiency, poor lipid profile, and higher risk of fatty liver disease. However, there were fewer large-scale research studies available to establish the safety of following a ketogenic diet for weight reduction. Numerous ketogenic diet research studies employed a significant caloric deficit rather than nutritional content, which has a greater impact on weight reduction. More extensive clinical trials are required to discover the optimal fat-to-nutrient ratio, calorie intake, and ketone body concentrations for weight reduction. More randomised, controlled research on the physiological and metabolic effects of food composition is required to establish the safety profile of the ketogenic diet in weight reduction and obesity treatment.

Current review highlighted the advantages of intermittent fasting, including its superiority in terms of waist circumference and central fat distribution in obese individuals over the ketogenic diet and other calorie-restricting regimens. Because intermittent fasting has a major role in regulating the quantities of certain proteins associated to lipid metabolism, it increases the production of HDL-cholesterol particles and triglyceride lipolysis, which lowers plasma total triglyceride levels. Additionally, it increases β-hydroxybutyrate, which in turn elevates ketone levels, reduces oxidative stress, and maintains lean muscle mass. The diversity of the research studies that have already been conducted makes it challenging to compare IF to other weight-loss strategies. In spite of the lack of information about its long-term sustainability and possible health effects, intermittent fasting seems to be a viable primary care strategy for obesity. Further investigation is necessary to ascertain how IF could complement effective weight-loss methods.

In conclusion, it has been found that prolonged, sporadic fasting increases the generation of ketones similar to a ketogenic diet. Thus, combining intermittent fasting with a ketogenic diet can help obese people control their weight over the long run. Though there hasn't been much study on the possible health effects of combining intermittent fasting with a ketogenic diet. Consuming a ketogenic diet during intermittent fasting seems to be a primary care strategy for obesity management. It is imperative to do further clinical research in order to discover novel weight management solutions for individuals suffering from obesity and other metabolic problems.

ACKNOWLEDGEMENT

I am grateful and thankful to the principal Dr. M. Ganga Raju and management of Gokaraju Rangaraju College of Pharmacy, Hyderabad for giving an intense support and assistance throughout the review.

Conflicts of interest

Regarding this review, the authors have no conflicts of interest.

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