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An Assessment on Recent Developments to Preclude Scepticism on Intermittent Fasting (IF): Probing the Basic Effects of IF on Physiological, Metabolic, And Cardiovascular Health

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KEYWORDS

Intermittent fasting, abstinence, health benefits, drawbacks, latest updates

ABSTRACT:

Background: The phrase "intermittent fasting" refers to a range of eating habits that alternate between times of eating and fasting, or abstention from foods. A common dietary strategy that is based on scheduled fasting intervals is called as intermittent fasting.

Major findings: Modern research has provided insight into intermittent fasting although people have fasted for millennia, since it is becoming a dubious as there are misconceptions rolling around due to lack of understanding and awareness. Current human studies indicate that intermittent fasting may lower the risk of cardiovascular disease with improvements in weight control, hypertension, dyslipidaemia, and diabetes, despite a lacuna of large-scale trials investigating the relationship between intermittent fasting and cardiovascular outcomes. Time-restricted eating, or intermittent fasting has gained popularity in recent years. It has many potential long-term health benefits and shows promise as a new paradigm in the fight against inflammation and weight loss.

Conclusion: In the present review, the authors tend to explore their perspective by analysing the facts of intermittent fasting and its thwack on human physiology in particular to metabolic activity and heart. It also highlighted the latest research updates on the upsides and downsides of intermittent fasting which gives clarity on diet restrictions without deprivation of nutrients.

Background:

Fasting is an ancient tradition which has been practised by various cultures and religions over centuries and our ancestors practised intermittent fasting due to food scarcity **(1).** One of the most well-liked health and fitness fads in the world right now is intermittent fasting (IF). Some say that IF has made their lives simpler, helped them lose weight, and improved their health. Restricting the daily food intake to a specific window of time is known as intermittent fasting **(2).** It has gained popularity as a means of losing weight and enhancing general health. Dietary restriction (DR) can be accomplished in one of two ways: by cutting back on food consumption without being hungry, or by excluding particular food items from the diet or reducing the quantity **(3).** In the long run, to influence the molecular mechanisms behind cellular aging as well as treat and prevent age-related illnesses DR can induce a state of "survival mode" in our cells, allowing them to repair aging-related damage.

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Although the long-term consequences of DR on human lifespan are still unknown, there is compelling evidence that animals fed this diet, from worms to monkeys, live longer **(4).** There might be a potential extension of life and lower the risk of age-related disease by implementing dietary restriction, which is an effective and cost-free method. But there are a variety of food restriction techniques, and not all of them are created equal in terms of advantages, drawbacks, and feasibility. Here, in the review we concentrated mostly on one of these techniques—intermittent fasting and try to enumerate the benefits, drawbacks and limelight was propelled on heart health **(5).**

Dietary restriction can be broadly classified into three categories:

- restricting calories (usually between 20 % and 40 % less than intake)
- restricting certain dietary components (like protein)
- fasting (a substantial reduction or elimination of food intake over a period of time).

All of the aforementioned techniques have been linked to positive health effects in people; however, the first two may not be the best options due to some disadvantages. Humans that reduce their calories for an extended period of time may have undesired weight loss, while mice (pre-clinical studies) that restrict their calories even more may become more vulnerable to certain viral diseases. Since low protein intake is linked to increased frailty and disease in those over 65, strategies like protein restriction may not be appropriate for older people **(6).** Dietary restriction methods such as fasting are becoming more and more effective and safe. The effects of continuous calorie restriction have been the focus of previous DR research; however, fasting offers an alternative strategy in which shorter bursts of restriction are interspersed with times of unrestricted eating **(6).** This indicates that fasting does not always need a reduction in total caloric intake—it is possible to fast one day and then ingest the equivalent of two days' worth of calories the following—though this is rarely the case in real life.

Although intermittent fasting (IF) has been used as a weight loss strategy for a long time, it gained a significant popularity in 2012 by BBC broadcast journalist Dr. Michael Mosley's TV documentary *Eat Fast, Live Longer* and book *The Fast Diet*, Kate Harrison's book *The 5:2 Diet* based on her own experience **(7,8,9).** The Obesity Code, written by Dr. Jason Fung in 2016, and her personal experience served as the inspiration for the 5:2 Diet. Positive chatter about IF kept growing as testimonials to its efficacy spread **(10).** Hypothesized mechanisms behind the reduction of cardiovascular risk factors by intermittent fasting are the three primary ideas that are the Oxidative Stress Hypothesis, Circadian Rhythm and Ketogenic State. According to the Oxidative Stress Hypothesis, fasting lowers stress, which in turn produces fewer free radicals and less mitochondrial energy, which in turn lowers oxidative stress in the body **(11).** The Circadian Rhythm component aims to maximize the consumption of fat and glucose by coordinating feeding times with the circadian rhythm of the organ **(12).** The third mechanism, known as the "ketogenic state," acknowledges that intermittent fasting causes the production of ketones, which lowers blood pressure and fat mass **(13).** According to latest updates, there are few contentious and chaos statements that are making people to reconceptualize about the intermittent fasting. The current review explored an understanding on the effects and influence of IF on cardiovascular health, physiological changes and metabolic needs.

Primary method of fasting:

Periodic fasting (PF) and intermittent fasting (IF) are the two main methods of fasting, these approaches are mostly distinguished by the length and frequency of the fasting period. Depending on how long and tight the fasting phase is, intermittent fasting entails drastically reducing or eliminating caloric intake for anywhere from 12 to 48 hours **(14).** This type of fasting is typically performed once a week or more. Some of the most popular methods of intermittent fasting include – firstly, an alternate day fast (ADF) with absolute abstinence. Secondly, adapted fasting on alternate days: extremely minimal calorie intake every other day. Thirdly, a 5:2 diet entails fasting or extremely low caloric intake (500-700 kcal) for two days per week (not needed in that order). Last comes a Time-restricted feeding, where limited food consumption to a set period of time per day, typically ranging from six to twelve hours is followed **(14). Figure 1** illustrated the effect of fasting after 24-hour period – might have a beneficiary effect such as mobilization of fat, declined blood glucose levels as liver glycogen breaks down.

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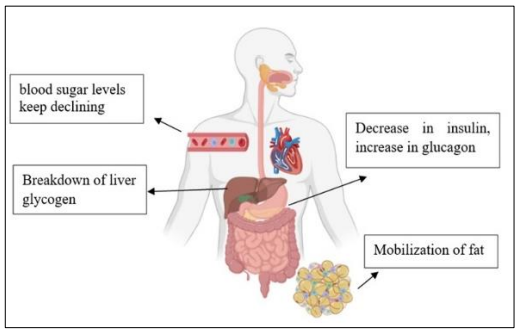

Fig. 1 Changes take place following a 24-hour fast - Glucose from glycogen storage turns to body's major fuel source.

Fasting for >18 hours per day inclined to Autophagy

Autophagy is a cellular recycling system of the body meant to recycle damaged and outdated cell components **(15).** When the cells are under stress or aren't getting enough nourishment, a natural cleansing process starts. The potential for autophagy to prevent and combat disease is being investigated by researchers. Fasting deprives one's body of nutrients, forcing it to repurpose cell components to function. Age and lifespan are linked to autophagy, a conservation mechanism that maintains energy homeostasis and cellular fitness through the catabolic breakdown of intracellular components. IF, or calorie restriction, is an autophagy activator. Additionally, a number of illnesses, including diabetes, cancer, vascular disorders, and many more, are linked to dysregulation of autophagy. By reducing inflammation and promoting autophagy, intermittent fasting (IF) has been linked to increased longevity and health **(16).** A study was performed for 30 days, with 25 healthy young males who were fasted for 17–19 hours per day. Blood samples were collected prior, and at subsequent intervals according to the study protocol for determination of ATG5, ULK1, and BECN1 which are contributing proteins and components in the autophagy process. The study concluded that the IF might lead to autophagy mechanism by altering the above factors, thus prolonging the longevity of an individual **(17)** as shown in Figure 2.

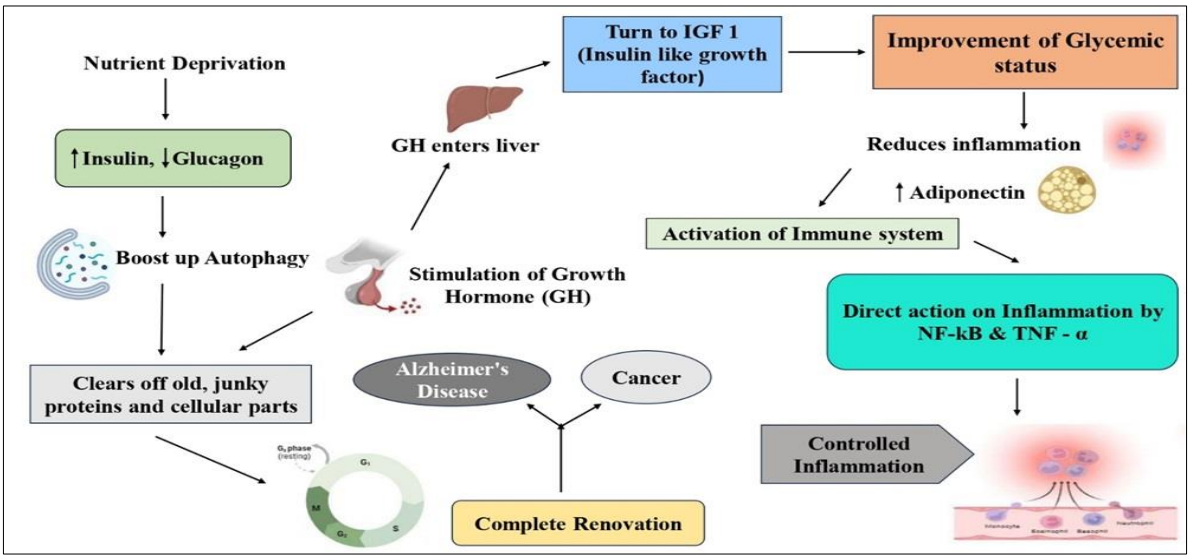

Fig. 2 Integration of autophagy and inflammation in 18 hours fasting

When the fasting is continued for a day or more than a day up till 72 hours, there are certain physiological changes that alter both glucogenesis and lipolysis. Total ghrelin levels are declined, with active PPAR – α, thereby raised ketones in the blood (as shown in the **Figure 3**). Ghrelin is an orexigenic gut peptide, the "hunger" hormone that signals the start of a meal. Blood glucose levels have an impact on plasma ghrelin and insulin levels because elevated glucose inhibits ghrelin release and increases insulin secretion **(18).** In *in vitro*, ghrelin also prevents insulin's effects on gluconeogenesis and glycogen production. Ghrelin may also increase the

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release of counter-regulatory hormones such as growth hormone (GH), cortisol, adrenaline, and (potentially) glucagon while inhibiting the insulin-sensitizing protein adiponectin from adipocytes **(19,20).** To fully understand ghrelin's physiological function in controlling glucose homeostasis, more research is required.

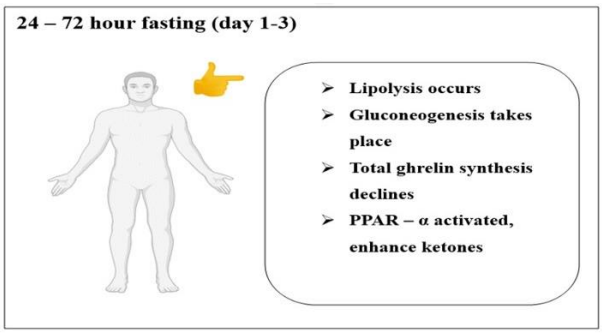

Fig. 3 A 1- 3-day fast's changes. When fat reserves are depleted, ketone bodies created become a primary energy source. From non-carbohydrate sources, a tiny quantity of glucose is created for the brain to use.

In the **Figure 4**, the consequences of fasting for 3-5 days (72-120 hours) causes rise in the β-hydroxybutyrate (BHB) which is an indicative of ketoacidosis. Insulin like growth factor (IGF-1) is basically produced in liver, skeletal muscle, and many tissues as a response to growth hormone, encourages the development of lean muscle mass and the formation of bones and other structures. Physiologically, to understand fully ghrelin's physiological function in controlling glucose homeostasis, further research is needed **(15).**

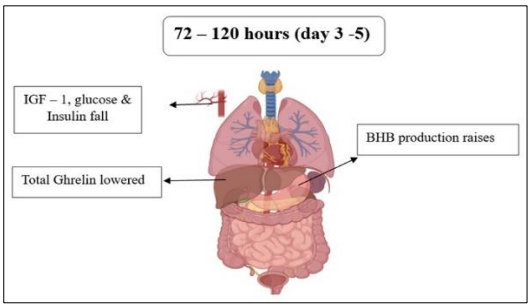

Fig. 4 The modifications of a 3–5 day fast - Ketosis reaches a stable state

Table 1 Effect of Intermittent fasting on distinct functions of body in hourly basis

S. No	Hours	Consequences/functions
1	>18 h	Cellular cleansing mechanism initiates, lead to Autophagy
2	24 h	✓ Fat mobilizes ✓ Blood glucose drops ✓ Liver glycogen breaks down
3	>24-72 h	✓ Lipid breaks down ✓ New glucose generates ✓ Ghrelin synthesis ✓ PPAR – α activated
4	72- 120 h	✓ BHB production ✓ Fall in insulin levels ✓ Drop in blood glucose

Intermittent Fasting's Effect on Heart Health

In the current world, cardiovascular problems are a major concern. Data from the World Health Organization (WHO) indicate that 17.9 million fatalities annually, or almost one-third of all deaths, are attributable to cardiovascular disorders which is the leading cause of death **(21).** Those over 45 years are the most commonly affected. One of the biggest risk factors for the onset of cardiovascular disease and other metabolic syndromes, such as diabetes, is obesity and being overweight. Making lifestyle changes, such as giving up smoking, getting more exercise, or maintaining a healthy weight,

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lowers the risk of cardiovascular disease. Changes in food are a significant modifiable component in the global obesity epidemic. The growing obesity pandemic prompted researchers to look for novel and practical dietetic approaches that would lower body mass and cut calories. The intermittent fasting (IF) diet is becoming more and more well-liked right now. When compared to more conventional approaches of calorie restriction, it is thought by many to be less restrictive **(16).** It entails combining short-term, stringent calorie restriction with a regular daily caloric intake. Meals are only eaten throughout a day or a week that is precisely defined. The ADF diet, or alternating day fasting, is a variation of the IF diet. It involves switching between the so-called "fast day" and the "feeding day," which occur on days when the energy limit is 75%. It is possible to lose weight and protect the heart by using IF **(22).** The reduction of fat tissue, particularly visceral fat tissue, the elevation of adiponectin concentration, and the reduction of leptin and low-density lipoprotein (LDL) concentration are likely responsible for the cardioprotective effects of the ADF diet **(23).**

Influence of Intermittent fasting on Physiologic and Metabolic functions

Due to the increased prevalence of obesity and metabolic syndrome (MetS) worldwide, the medical profession is placing a greater emphasis on developing novel treatments to counteract these conditions' pathophysiological effects. In the alternative day fasting, the circadian rhythm is the primary mechanism that regulates the balance between anabolic and catabolic processes during a 24-hour period **(24).** A balance between mRNA and proteins regulates several elements of metabolism including as glycolysis, protein synthesis, lipid synthesis and oxidation, gluconeogenesis, and mitochondrial activities, is crucial for the daily fed-fast cyclical rhythm. A group of positive outcomes prepondarate, such as reduced body weight, body fat, blood pressure, blood glucose, triglycerides, glucose tolerance, and inflammatory markers as a consequence of time-restricted eating. An individual gains familiarity with fed, post-absorptive, and fasting phases during the intermittent fasting program. Insulin is the key driving hormone when the body is feeding and using glucose as fuel; and glucagon is the primary hormone when it is fasting, and the body uses its reserves of glycogen from the liver as fuel. The point of negative energy balance at which the liver's glycogen stores run out and fatty acids begin to be digested is known as the commencement of the metabolic switch **(25).**

Link between Intermittent fasting and Inflammation:

A correlation exists between obesity and low-grade inflammation. It has been demonstrated that dietary restriction leading to weight loss lowers systemic inflammation. Although intermittent fasting has been more well-liked lately as a weight-loss strategy, its impact on inflammatory markers needs to be elaborated **(26).** In the process of starving, through adiponectin secretion, there is a direct action on Inflammation by NF-kB & TNF – α, a controlled inflammation is created (Figure 2). Pre-clinical studies demonstrated decline in inflammation with intermittent fasting and calorie restriction and promote cancer while also increasing life expectancy **(27).** Intermittent extended fasting throughout the month of Ramadan (RIF) was thought to have a favourable impact on inflammation **(28).** To find out the effect of RIF, specific inflammatory cytokines and immunological biomarkers in healthy participants was evaluated in a cross-sectional study. To investigate the circulating proinflammatory cytokines (interleukin [IL]-1β, IL-6, and tumour necrosis factor α), immune cells (total leukocytes, monocytes, granulocytes, and lymphocytes), and anthropometric and dietary measures, 50 healthy volunteers (21 men and 29 women) who fasted during Ramadan were enlisted. The studies were carried out one week prior to the start of the Ramadan fast, at the conclusion of the third week, and one month following the end of the month **(28).** Systolic and diastolic blood pressures, body weight, body fat percentage, and the proinflammatory cytokines IL-1β, IL-6, and tumour necrosis factor α were all significantly lowered ($p < 0.05$) during Ramadan than they were either before or after or following the end of the Ramadan fast **(29).** Although they still fell within the standard ranges, immune cells dramatically declined during Ramadan. This particular study emphasized the effect of IF on the inflammation and projected that IF is protective in terms of inflammation as this is the main culprit for many diseases and disorders. As inflammation stands as a key factor for many of the chronic diseases and disorders it is imperative to focus on this aspect so as to prevent the tissue injury if left ignored or crude. Also try the best ways to prevent and take few prophylactic steps to combat the associated pathological conditions.

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Beneficial effects of Intermittent fasting

All of the previously suggested techniques for intermittent fasting have demonstrated notable advantages on a range of biomarkers, often surpassing those of calorie restriction. For instance, there are positive effects of alternate-day fasting on markers of inflammation, cardiovascular health, and low-density lipoprotein (LDL), or "bad cholesterol." It decreased fat mass as well. This was the case for both short-term (4 weeks) and long-term (6 months) fasting patterns in healthy, non-obese people. For those with metabolic diseases and those who are overweight, other intermittent fasting techniques have also shown promise. Time-restricted feeding prevents weight gain, enhances sleep, lessens cardiovascular issues associated with aging, and strengthens the body's blood sugar regulation capabilities **(30).** Limiting food intake to an 8-hour window for six weeks did not enhance cardiovascular function in healthy middle-aged and older adults, but it did somewhat improved blood sugar control and had no effect on lean mass. Intermittent fasting boosted up thinking and memory, improved blood pressure, aids in fat loss with well maintenance of muscle mass. The majority of the research to date indicates that intermittent fasting can reduce insulin resistance, lower levels of leptin, increase levels of adiponectin, and help people lose weight while also lowering their fasting glucose, fasting insulin, and leptin levels. According to certain research, some individuals were able to stop needing insulin medication by engaging in intermittent fasting under the guidance of their physicians **(25).**

Downsides of Intermittent fasting

An intermittent fasting pattern does not follow random timings; rather, it is based on a predetermined schedule Trusted Source. Nevertheless, every person's experience with intermittent fasting is unique, and different approaches will work for different individuals **(31).**

Over eating and potential weight gain

Some people may overeat during eating periods if their intake is limited to 8 hours per day, hoping to make up for the hours they spent fasting. Unhealthy eating habits, digestion issues, and weight gain could result from this. It's interesting to note that existing data doesn't support the idea that intermittent fasting promotes weight loss any more than standard diets that call for total calorie restriction. A little weight loss may result from either eating style **(32).**

Short-term physical symptoms

At the beginning, 16/8 intermittent fasting, unpleasant side effects like exhaustion, weakness, and hunger may be experienced.

Menstrual cycle and hormonal fluctuations

To completely comprehend the effect of intermittent fasting on women's reproductive health, human research data is required. Moreover, postmenopausal people could react differently to intermittent fasting. Weight gain and decreased insulin sensitivity are the two effects of menopause that may be mitigated by intermittent fasting **(33).**

Association of Intermittent fasting with Cardiovascular risk

Insulin resistance is associated with an increased state of inflammation, which includes raised CRP, decreased adiponectin, decreased low-density lipoprotein (LDL) particle size, and other metabolic variables linked to the development of coronary artery disease and atherosclerosis **(34).** Moreover, insulin raises the risk of fluid retention and congestive heart failure in addition to being linked to atherogenic dyslipidaemia **(35).** Therefore, it would be expected that cutting insulin levels with intermittent fasting will lower serious adverse cardiovascular events. Studies on the onset of atherosclerosis have validated the benefits of the IF diet. Atherosclerotic plaque is prevented from developing by intermittent fasting by lowering the levels of inflammatory markers such as C – reactive protein (CRP), homocysteine, and IL-6 **(36).** Recently, research was conducted in Chicago regarding the impact of intermittent fasting on cardiovascular health, also discussed in the current review **(37).**

Updated Research on Intermittent fasting

Intermittent fasting has been connected in recent studies to a higher risk of cardiovascular disease death, but study has not yet been published in a peer-reviewed publication, though it was presented by researchers at a recent American Heart Association meeting **(38).** Medical experts have expressed concern about the results, advising caution when interpreting the study. Francisco in April 2, 2024 analysed about the link

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between IF and increased heart risk, draws an attention because of cynicism from the medical professionals, needs more assessment as the proofs are lacking and unclear. However, with the existing heart related ailments and other diseases like cancer and other chronic disorders **(39).**

On March 18th 2024, American Heart Association published an authentic information about IF and its effects on cardiovascular Health. A preliminary research presented at the American Heart Association's Epidemiology and Prevention/Lifestyle and Cardiometabolic Scientific Sessions 2024, March 18- 21, in Chicago **(38).** It emphasized that those who adhered to an 8-hour time-restricted eating regimen, a form of intermittent fasting, had a 91% higher chance of dying from cardiovascular disease, according to a study involving over 20,000 participants. Cardiovascular mortality was also more likely in those with cancer or heart disease. Restricting food intake to less than 8 hours per day did not appear to be connected with a longer lifespan when compared to a regular schedule of eating across 12–16 hours per day. In the previous research, Time-restricted eating has been shown to enhance blood pressure, blood glucose, cholesterol, and other cardiometabolic health indicators **(26).** Researchers looked into the possible effects of an 8-hour time-restricted eating regimen on long-term health in this study. They compared data from the Centres for Disease Control and Prevention's National Death Index database, which contains information on deaths in the United States from 2003 to December 2019, with information regarding dietary patterns for participants in the annual 2003–2018 National Health and Nutrition Examination Surveys **(40).** Eating for at least eight hours a day, but not more than ten, was linked to a 66% increased risk of dying from heart disease or stroke in those who already had cardiovascular disease. Victor Wenze Zhong in the Department of epidemiology and biostatistics at Shanghai Jiao Tong University School of Medicine in Shanghai, China, stated that the long-term health effects of time-restricted eating such as the risk of cardiovascular disease or death from any cause are still unknown **(41).** Subsequent investigations could explore the molecular processes behind the correlations between a restricted meal schedule and unfavourable cardiovascular consequences. It is like poking holes on the effects and in the press release, Zhong, Epidemiology and Biostatistics, Shanghai Jiao Tong University School of Medicine, Shanghai, China, mentioned at *theheart.org | Medscape Cardiology* that the study simply demonstrates a correlation between the two and makes no claims that intermittent fasting raises the risk of cardiovascular death **(42).** However, an evaluation needed to observe long-term health effects. Figuratively, long observation/research sounds necessary and mandatory for the evaluation of safety of intermittent fasting in normal and accordingly in individuals suffering from chronic disorders.

Conclusions:

However, an increasing amount of evidence indicates that the timing of the fast is crucial and can help make intermittent fasting (IF) a more practical, long-lasting, and successful strategy for both diabetes prevention and weight loss. Obese and diabetic individuals have also shown the benefits of the IF diet. Body weight decreases when following the IF diet since less food is ingested. By boosting the B cells of the pancreatic islets, it also enhances glucose metabolism and raises tissue sensitivity to insulin. Additionally, the IF diet reduces heart hypertrophy. Whether these advantages are only attributable to weight loss or to other factors is still up for debate. Any diet that is successful relies on rule compliance, or adhering to a recommended diet in accordance with the circadian rhythm. The intermittent fasting diet has numerous advantages, but it also has some significant drawbacks. It is not advised for diabetics, pregnant or nursing women, or anyone with hormone imbalances to fast since it may be risky. Furthermore, it is not advised for those with eating problems, those with a BMI under 18.5, or those who are underweight to follow the intermittent fasting diet. The intermittent fasting (IF) diet and its variations have gained popularity in the past several years. This diet is beneficial for weight loss, but it's also a useful non-pharmacological therapy option. Numerous research conducted on humans and animals have demonstrated this. Before starting the IF diet, people should take into account their existing health and circumstances.

Abbreviations

PPAR – α – Peroxisome proliferator–activated receptor gamma

BHB – β-hydroxybutyrate

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IGF – Insulin Growth factor

NFkB – Nuclear factor kappa-light-chain-enhancer of activated B cells

TNF – α – Tumour necrosis factor

IL – Interleukin

CRP – C-reactive protein

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