

## REVIEW ARTICLE

### The Influence of Intermittent Fasting Regimens on the Regulatory Mechanisms of Metabolic Health

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#### Abstract

Intermittent fasting (IF) describes a variety of eating patterns during which no or few calories are consumed for certain time, which can range from twelve hours to some days, on a frequent basis. In recent years, IF became popular as a possible new paradigm for weight loss and inflammation reduction, as well as numerous health benefits. In this review, we incorporated various aspects of fasting, especially the effects of intermittent fasting diet (IFD) on lipid profile and inflammation as well as its effect on the body mass index and the glucose metabolism in non-diabetic people. Liver, cardiovascular and central nervous systems physiological responses are illustrated as well. An IFD may provide a huge metabolic benefit by improving glycemic control, insulin resistance, and adipokine concentration with a discount of body mass index in adults. Also, IF protocol helps improving several physiological functions thus inducing longevity and minimizing illness. Moreover, alternate day fasting (ADF) is considered as good protocol of food intake therapy for persons with non-alcoholic fatty liver disease (NAFLD), which can help in loss of weight and treatment of dyslipidemia within a relatively short period of time (a month to three months), and reduce cardiovascular risk factors. In conclusion, IF is suggested during the fight against many diseases as cancer, diabetes and central nervous system (CNS) disorders.

**Keywords:** Non-alcoholic fatty liver disease; Intermittent fasting; Alternate day; Calorie restriction; Lipid profile.

#### Introduction

For many people, intermittent fasting (IF) is taken under consideration to be less constricting as compared with traditional methods of calorie restriction [1], which includes consuming standard feeding every day in combination with adjusted restriction of calories [2]. Time of feeding is adjusted at certain definite times [3]. Various protocols of feeding are conducted to investigate IF effects [4]. The most popular protocol is time-restricted feeding. It is often utilized in three options: 16/8, 18/6 and 20/4. 16/8 is consisting of a 16 h fast, then an 8 h nutritional window. During a harder approach, the nutritional window is often shortened to 4 h [3]. Another protocol includes 24 h fasting period,

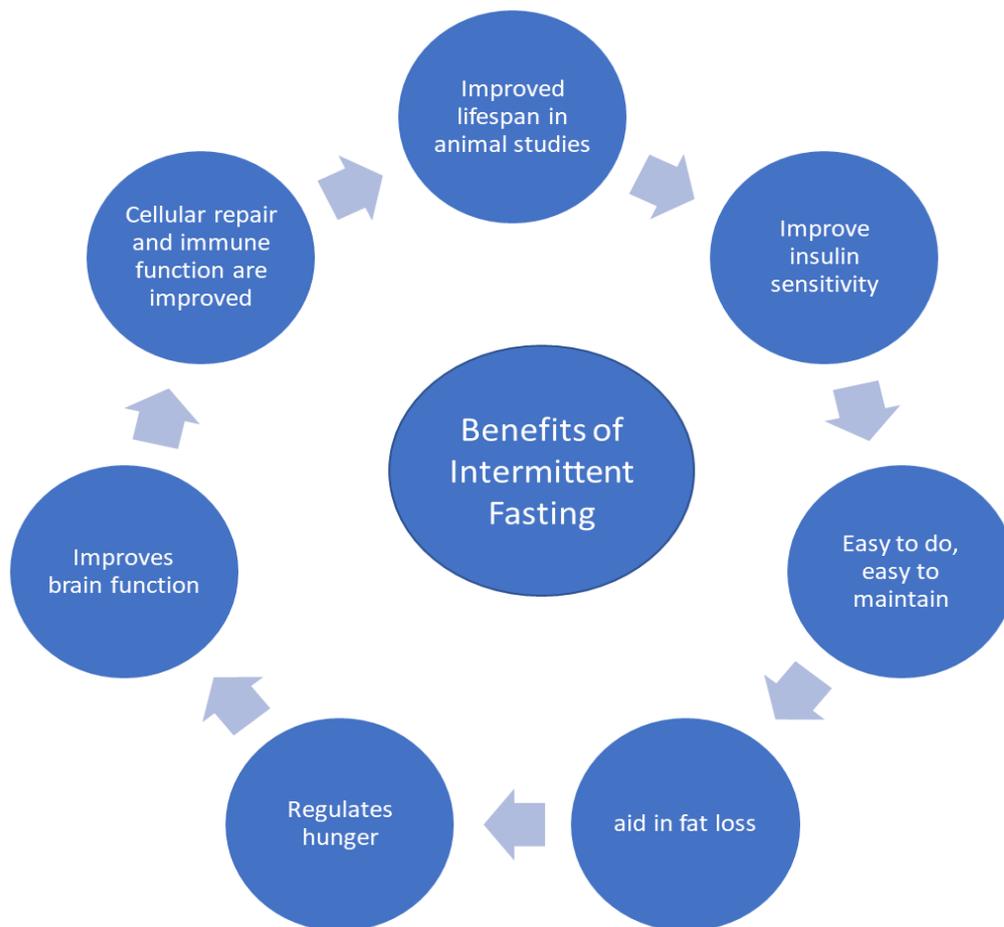
alternated with a 24 h feeding period (ADF). There are two possible systems, 5/2 or 4/3. Within the 5/2 system, the caloric restriction is employed for 2 days per week, and a daily diet for five days. Most of the people separate their fasting times [5]. A comparison between the feedbacks of the IF protocols (5/2 protocol) and the continual energy restriction (CER) protocol indicated that the IF protocol is more appropriate for having less weight and adjusted glycemic index in three months. Also, persons suffering from overweight are suggested to follow IF protocols to the extent of CER protocol [6]. Alternate day Modified Fasting (ADMf) is the eating pattern involving consumption of less than 25% of baseline energy needed on “fasting” days, alternated with a day of unrestricted food

intake or “feast” day. Finally, fasting for one to two days each week is known as periodic fasting [7]. Below, we are summarizing the beneficial effects of different IF protocols on health.

**Effects of IF on health and aging**

Intermittent fasting helps in systemic inflammatory diseases treatment [8], keeping safe against degeneration of neurons, and also increasing the lifetime [9]. Furthermore, the elevated adiponectin level, drop in the level of leptin and low-density lipoprotein cholesterol (LDL-c) are due to the decline of visceral fats during ADF providing a remarkable cardioprotective way [2]. Time-restricted feeding (TRF) is preferable by athletes as it helps losing weight without any change in the mass of muscles. Moreover, the two protocols of IF are good ways for healthy people who want to lose weight and to improve their

health [10]. In these protocols, intermittent energy restriction (ER) needs a level of energy restriction in certain times per week, so that it could be applied smoothly in comparison with continuous energy reduction (continuous energy restriction) [11]. Even though, for the treatment of obesity in adult persons, monotonous use of very low-calorie diets in the therapeutic regimen of obesity in adults is recommended. It I thought to be applied for three months in an intermittent or continuous manner [12]. Intermittent fasting protocol helps weight loss which decreases the risk of the development of cardiovascular diseases. As IF decreases arterial hypertension, obesity, insulin resistance, type II diabetes and improper diet [13]. the health benefits of IF are summarized in Figure (1).



**Figure 1: The health benefits of IF regimes**

## 1. Effect of IF on body metabolism

### a. Lipid metabolism and IF

Different organisms have established various mechanisms to permit them overcoming the times of starvation [14]. Mammals have an energy store in the liver and adipose tissue. This in turn permits them to endure the periods of food shortage [15]. Fats (the vital structures in our body) are different component structurally and functionally [16]. Energy is stored in the adipose tissues, then by the influence of lipases enzymes, it is released under certain conditions [17]. After consuming food, the glucose level elevates then within a short time, it decreases to the same level that was before eating. Ketones level is small, due to stored liver glycogen are still present [15]. During fasting times, changes in the metabolism inside cells are noticed [18]. While glucose is depleted, the cells of the body starts to use ketones, which are released from fatty acid transformations [19,20]. Following the ADF for two to three weeks, a noticeable decrease in body weight (about 3%), While longer ADF periods recorded a decreasing of 8% and a decline in visceral fat mass. Also, triglycerides, total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c) were decreased even in their concentrations or sizes. Also, it decreases the risk of the development of coronary heart disease (CHD) [21]. In a previous study, the results prove the efficacy of decreasing weight even though the concurrent consuming of high-fat and sugar diet [22] (Table 1).

### b. Body weight, glucose metabolism, and IF

The ideal management of obesity or even overweight is 1/5 to 1/3 calorie restriction (CR) with a wide range changing of lifestyle [23]. In recent times, IFD is a new manner to reach and keep loss of weight has gained popularity. In a meta-analysis, a decrease in body mass index and a leptin level reduction, as well as an elevation in adiponectin level were reported. Lean mass was relatively well-kept in the IFD group; however, no noticeable weight decrease was

identified. In previous studies, the overall weight reduction of both an IFD and a daily CR (by 0.15 to 0.60 of the usual caloric intake every day) were similar between the two groups [24]. Many challenges remain regarding to the effect of IFD on glucose metabolism. In previous studies, blood glucose was not affected by IF diets significantly [25]. Also, various recordings had noticed a 3 to 6% decrease in fasting glucose in prediabetic persons [26,27]. In healthy persons, fasting glucose concentration was not significantly affected [28]. The effect of IF vs a non-fasting control on fasting blood glucose (changes from baseline) in adult individuals without chronic metabolic illness as in Figure (2).

## 2. Effect of IF on body organs

### a. Liver

In the beginning of fasting, liver glycogen is consumed then the glucose is liberated for extrahepatic tissues by glycogenolysis. [29]. Most of studies on mice found that the biochemical and molecular responses of hepatocytes to IF are through TRF protocols either a high fat or normal diet [30,31]. TRF (four hours eating period each day) and normalization of circadian rhythms, help improving of glucose regulation and loss of weight in mice [32,33]. Also, in eight h/day, TRF counteracts the effect of high fat diet, which cause obesity in rats [31]. While, nine hours/day of TRF reduces the glucose concentration in a rat model of type I diabetes and increases the sensitivity of glucose [34].

### b. Cardiovascular system

Studies in mice and rats had recorded remarkable influences of IF (ADF) on blood pressure and heart rate [35]. In addition, rats conducted on ADF showed superior cardiovascular stress adaptation, which is translated in the form of heart rate elevation and reduced blood pressure through and after 60 minutes of hold stress [35]. It was recorded that rats kept on ADF for six months exhibit cardiac reserve reduction [36]. However, it is not obvious if this is because of a pathological case or is due to

the long period of decreasing heart rate and blood pressure in response to ADF [37]. Blood pressure rate changeability is also augmented due to ADF, because of boosted parasympathetic tone [36]. ADF impacts on blood pressure and heart rate changeability are similar to the impacts of endurance training [38].

### c. Central nervous system

In rats, TRF prevents the decrease in cognitive functions due to aging [39,40]. For instance, finding of 4/10 CR/TRF prohibited decrements in motor performance by aging (rotarod test) also maze learning (fourteen-unit T-maze) with rodents [41]. However, mechanism of IF in enhancing cognitive and motor performance of cognitively manner has not been well-known. The switch to ketone utilization is a key of biological mechanisms, which forestalls age-related declines in the integrity of the white matter and maintain memory [39]. Suggestions provide other mechanisms by which IF may preserve as well as boost cognitive function by coming older. Such as, even in normal weight or obese rats conducted on 4/10 CR/TRF for 12 weeks showed an elevated density of dendritic spines in hippocampal dentate granule neurons, and that elevation in synapse numbers is associated with an elevated concentration of brain-derived neurotrophic factor (BDNF) [42]. It has been established that BDNF have vital contribution in memory, learning and mediates antidepressant, anxiolytic impacts of antidepressant medications and exercises [43,44]. BDNF signaling can provide essential contribution in the development of synaptic plasticity through IF [45].

## 3. Effect of IF on some animal diseases

### a. Diabetes

Rats fed a high fat diet develop insulin resistance and diabetes, which can be improved by keeping them up on an eight h/day TRF diet [46]. Essentially, when mice are conducted on a chow of high fat diet, they gain higher weight, systemic inflammation and hyperinsulinemia, which are all decreased by restricting food

availability to eight h/day [46]. The latter anti-diabetic effect of TRF isn't related to caloric restriction because mice provided food for less than 8 h/day consume an equivalent amount of food as control mice fed ad libitum. Similar to leptin-deficient mice and leptin receptor mutant mice, mice with reduced BDNF levels are hyperphagic and develop insulin resistance and diabetes [47]. In case of BDNF administration by intraperitoneal injection to leptin receptor mutant mice, diabetes and high weight are reversely changed [48]. Also, in the case of applying ADF protocols in mice with diabetic BDNF+/-, the blood concentration of leptin, insulin and glucose are decreased [49]. Intermittent fasting may upgrade the insulin deficit and glucose intolerance in type I diabetic rats through a mechanism of pancreatic  $\beta$ -cells conservation [50]. The augmentation of cellular stress resistance through the protocols of IF keeps  $\beta$  cells, as recorded in the intermittent fasting impacts on neurons and myocardial cells [51,52]. Mechanism through which intermittent fasting reverses, prevents diabetic cases includes elevation sensitivity of insulin receptor signaling and by this way insulin immediately stimulates glucose uptake by hepatocytes and myocytes and several types of cells like neurons [53]. Changes in other signaling pathways affected by IF in one or many cell types may include decreasing of mTOR signaling; ameliorated mitochondrial function; mitochondrial biogenesis enhancement; and up-regulation of, BDNF, cAMP response element -binding protein (CREB) and pathways of autophagy [54-58].

### b. Cardiovascular diseases

In a model of myocardial infarction (MI; coronary artery ligation), rats that had been kept on ADF for 3 months prior to MI, exhibited a reduced myocardial infarct size and the number of apoptotic cells in the area at risk (penumbra) was decreased by around 3/4 compared to the ad libitum control rats [59]. In the analysis of rats conducted on ad libitum diet left ventricular remodeling and infarct expansion happened but those conducted on the ADF protocols protection

against MI-induced damage takes place [60]. In addition, ADF in Lamp2-deficient mice worsened myocardial damage, suggesting that enhancing autophagy is well related to alternate day fasting cardioprotective impacts [61]. Intermittent fasting protocols were documented to highly developing of recovery and survival of myocardial functions in rodents when introduced fourteen days after myocardial infarction by obstruction of the left coronary artery [62]. Whereas quite 3/4 of the rats on the ADF diet survived during the eight-weeks post myocardial infarction period, but 1/4 of the rats on the traditional ad libitum diet survived. Data from the later study suggested that the mechanism of action of IF is consistent with the intervention of adaptive cellular stress responses where the levels of Hypoxia-inducible factor1 alpha (HIF-1 $\alpha$ ), Brain-derived neurotrophic factor (BDNF) and Vascular endothelial growth factor (VEGF) were significantly increased in myocardial tissue of rats on IF compared to those on the control diet.

### c. Cancer

Lately, some investigations in rodents have clarified that periodic fasting (PF) for two or more days may have an impact as chemotherapy in delaying the development of a wide variety of cancers. Furthermore, while sensitizing cancer cells to the treatment, it has protection for normal cells against the toxic influences of chemotherapy medications [62-66]. Highly restricted feeding that shows effects as PF had high influences in producing great decline in the occurrence of the tumor, moreover it decreases tumor sites numbers, providing a decrease of metastatic cancers [67]. Scientists have investigated the contribution of periodic fasting in prohibition of cancer and curing [9, 68]. Intermittent fasting was reported in murine cancer types, however the majority of cancer were inhibited. ADF effects on the existence of three-month-old tumor-free and tumor having rats; half of ADF rats stay alive until day 10 in comparison with 1/8 existence in the control group [69].

Another research showed that a one day per week IF diet resulted in only an 8% decrease in IGF-1 levels, which may show in part its limited efficacy [70]. Regarding the recent development of relatively high calorie fasting modified diets (FMDs) tested in both mice and humans [71]. More studies on IF and cancer handling were thought to take in consideration the potential toxicity of their association with chemotherapy, especially in eating periods, that can induce a rise within the spread of different cell kinds and encourage the group of secondary tumors. Also, it is necessary to express if intermittent fasting protocols have an effect on the metabolism of chemotherapeutic agents, as this could affect the impact of the drug treatment on the cancer cells.

### 4. Effect of IF on dyslipidemia in patients with non-alcoholic fatty liver disease

The influences of ADF protocol on nonalcoholic fatty liver disease (NAFLD) patients was reported to be tolerable, safe protocol for NAFLD cases. Also, it reduces body weight, total cholesterol, fat mass and triacyl glycerol (TAG). Modifications of lifestyle are basic management of NAFLD, because protocol of feeding and physical training stimulates loss of weight and ameliorates steatosis. The components of food are a necessary issue to be taken in consideration for instance taking carbohydrates instead of fats can decrease the content of intrahepatic lipid [72, 73]. Previous investigations of NAFLD reported that minimally 0.05 of body weight is lost in association with development of steatosis, insulin resistance, but minimally weight loss of about 0.07 is needed for relieving inflammation [74,75]. When IF is administered over a period of two to twelve weeks, it results in a modest weight loss (0.02 to 0.10). Also, TRF has significantly reduced BMI and has been reported as a potential cost-effective intervention in cases who suffering from obesity and NAFLD in another research [76]. Nevertheless, the weight loss not significant so further investigations are required to assign the influences of TRF on NAFLD cases [77].

The application of ADF protocol resulted after 4 weeks of dietary intervention in about 0.06 weight loss was noticed and after 12 weeks, further 0.05 weight loss was observed. Eventually, this loss in weight of the body was basically due to a loss in fat mass associated with no modifications in the fat-free mass noticed. Noticeably, population in ADF protocol exhibited slight hyperphagic feeling on feast times as a compensatory mechanism in fast times [78, 79].

### Conclusion

Intermittent fasting improves glycemic control and insulin resistance with a reduction in BMI, and an increase in serum adiponectin concentration. Also, it may decrease in the oxidative stress, improvement in the total antioxidant capacity and the lipid profile. Also, IF is effective manner in avoidance of many diseases like CVS diseases, hyperlipidemia, cancer and diabetes

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## الملخص العربي

## تأثير أنظمة الصيام المتقطع على الآليات التنظيمية للصحة الأيضية

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يصف الصيام المتقطع (IF) مجموعة متنوعة من أنماط الأكل التي يتم خلالها استهلاك سعرات حرارية قليلة أو بدون استهلاك اي منها لفترة معينة ، والتي يمكن أن تتراوح من اثني عشر ساعة إلى بعض الأيام ، على أساس متكرر. في السنوات الأخيرة ، أصبح IF شائعًا كنموذج جديد محتمل لفقدان الوزن وتقليل الالتهابات ، بالإضافة إلى العديد من الفوائد الصحية. في هذه المراجعة ، قمنا بدمج جوانب مختلفة من الصيام ، لا سيما آثار نظام الصيام المتقطع (IFD) على ملف الدهون والالتهابات وكذلك تأثيره على مؤشر كتلة الجسم واستقلاب الجلوكوز لدى الأشخاص غير المصابين بالسكري. كما تم توضيح الاستجابات الفسيولوجية للكبد والقلب والأوعية الدموية والجهاز العصبي المركزي. قد يوفر نظام الصيام المتقطع فائدة استقلابية كبيرة من خلال تحسين التحكم في نسبة السكر في الدم ومقاومة الأنسولين وتركيز الأديبوكين مع خصم مؤشر كتلة الجسم لدى البالغين. أيضًا ، يساعد بروتوكول الصيام المتقطع على تحسين العديد من الوظائف الفسيولوجية مما يؤدي إلى إطالة العمر وتقليل المرض. علاوة على ذلك ، يعتبر صيام اليوم البديل (ADF) بروتوكولًا جيدًا لعلاج تناول الطعام للأشخاص الذين يعانون من مرض الكبد الدهني غير الكحولي (NAFLD) ، والذي يمكن أن يساعد في إنقاص الوزن وعلاج اضطراب شحميات الدم في غضون فترة زمنية قصيرة نسبيًا (من شهر إلى ثلاثة أشهر) ، وتقليل عوامل الخطر القلبية الوعائية. في الختام ، تم اقتراح الصيام المتقطع أثناء مكافحة العديد من الأمراض مثل السرطان والسكري واضطرابات الجهاز العصبي المركزي (CNS).