

Intermittent Fasting and Its Potential Effects on Health

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Abstract

This compilation study explains intermittent fasting, ways to practice it, and discusses its potential health effects, studies on intermittent fasting, and when to avoid practicing it. For many years, people have applied various diet models to lose weight, prevent nutrition-related diseases, and maintain high quality of life. Intermittent fasting has recently become a popular nutrition model, and it has been shown to have positive effects on several metabolic processes, particularly on the loss of body weight. Intermittent fasting is the restriction of energy or food intake on certain days of the week, day, or specific time, and there are different ways to perform it. Alternative day fasting is a method in which around 25% of the energy needs are met and then the other meal is consumed after a 24-hour fasting period. In the modified fasting regime, around 20-25% of the daily energy needs are met on non-successful two days of the week. The time-restricted eating model is the most common regime in which the daily energy intake is compacted into 8 hours with 16-hour abstinence. Ramadan fasting is an act of abstinence from all food in Islam from dawn until sunset. Unlike other fasting methods, fasting is conducted for religious purposes only, where no food or drink is allowed regardless of the energy content. Alternative day fasting, modified fasting regime, time-restricted eating, and Ramadan fasting are some of the intermittent fasting methods. Although intermittent fasting seems like an alternative diet model for losing body weight, it has many positive effects on heart health, insulin resistance, brain health, cancer, metabolic health, inflammation, and aging, all of which can be explained by the various effects of intermittent fasting. Ketone bodies, which are the fuel of the brain and body during fasting and long-term exercise, increase during hunger. They are not only a source of energy but also facilitate many metabolic events in tissues and cells. It also affects the circadian rhythm when intermittent fasting is associated with the circadian rhythm because it limits food intake at certain times. Eating late at night disturbs circadian rhythm and may cause chronic diseases like obesity, diabetes etc. the intermittent fasting also has effects on the microbiota, and studies revealed that intermittent fasting improves the gut microbiota diversity and good gut bacteria with benefits on gut health. Similar to any other diet, intermittent fasting may vary with age, sex, and special condition (pregnancy, breast feeding, adolescents etc., or it is not recommended for specific circumstances.

Keywords: Intermittent fasting, time restricted fasting, fasting, metabolic diseases

INTRODUCTION

Fasting is the voluntary abstinence from food for a limited time, which people practice for centuries due to various reasons. A diet model is used for therapeutic purposes with varying ways of practice according to religion and ethnic origin.^{1,2} Intermittent fasting is a nutrition model that differs from religious fasting that aims to attain spiritual satisfaction. Unlike religious fasting, consumption of non-energy beverages is forbidden.^{3,4} Intermittent fasting is effective for weight

loss because it causes less energy intake or hunger for a certain period. Fasting lowers insulin levels in the body. Low insulin levels allow the use of stored fat. In addition, autophagy is triggered when cells are hungry, which cleans the damaged cells. Fasting also influences growth hormone levels, increasing growth hormone levels, leading to fat burn and muscle increase.⁵

Obesity, which has become increasingly common worldwide, causes the incidence and progression of many diseases, particularly cardiovascular

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diseases, cancer, and hypertension⁽¹⁾. Intermittent fasting may help with weight loss, metabolic health, decreasing inflammation, advanced immunity, decreasing cholesterol, protection against neurodegenerative diseases, better cognitive performance and mental status, aging, and improving sleep quality⁽¹⁰⁾.

Methods

This study is a compilation of previous studies. This study has not been applied to any animals or humans. No patient informed consent form was obtained.

The Types of Intermittent Fasting

Alternative Day Fasting: A Short Form

Alternative day fasting includes meeting 25% of energy intake on the days of fasting and eating as desired on the other days. One has a meal at their preferred time and then stops eating for the next 24 hours; they may consume no-energy drinks. For instance, an individual who has the first meal at 06.00 p.m. does not eat until 06.00 p.m. the next evening but may drink energy-free beverages (tea - coffee - herbal tea without sugar, sparkling water, etc.) alternative day fasting may have a positive influence on weight loss and treatment of vascular health.⁴

Short-term studies on the effect of alternative day fasting covering 2-3-week period revealed that triglyceride levels and consequently body mass decreased by 3%, while long-term studies reflected that weight loss was higher by 8% when compared with the initial weight; visceral fat rate reduced and low-density lipoprotein (LDL) cholesterol and triglyceride levels improved, respectively.⁶ However, studies on pessimist mood, low attention span, and low work performance.

⁽¹⁾<https://hsgm.saglik.gov.tr/tr/obezite/dunyada-obezitenin-gorulmesikligi.html>

⁽¹⁰⁾<https://www.sleepfoundation.org/physical-health/intermittent-fasting-sleep>

On days of fasting^{2,7} while While studies conducted on animals have concluded that alternative day fasting reduces cardiovascular diseases, type 2 diabetes, and cancer risk, yet there are not sufficient data for human.⁸

Modified Fasting

This model is not about the total restriction on energy intake on fasting days but 20-25% of energy intake on 2 non-successive days in a week. On days of fasting, women consumed approximately 500 kcal/day and men 600 kcal/day, and they continued their regular diet on the other days. Modified fasting is also known as the 5:2 diet.⁹

Pursuant to the studies conducted to identify the influence of modified fasting on humans with a sample size between 10-107 pre-obese or obese adults, the control group practicing modified fasting experienced weight loss and a decrease in fasting insulin and glucose with improvements in LDL and triglyceride levels. Some individuals may find it challenging to adhere to certain fasting patterns, and there may be social or psychological implications worth considering. In terms of the effect on mood, very few participants showed several side-effects like feeling chill, uneasiness, low energy levels, and hunger, but positive effects like less tension, aggression, exhaustion, and confidence.^{4,10,11}

Time Restricted Eating

This is a type of intermittent fasting in which one eats at certain time intervals. This model particularly focuses on when food is consumed rather than what is consumed at all. The most common models are 16:8, 18:6, 20:4. The effect mechanism was based on adjusting metabolic times by affecting circadian rhythm. The most widely used model is 16:8, and the day is planned as around 8 hours for eating and drinking and 16 hours for fasting. This model generally plans 2 main meals and where necessary snacks in 8-hour period determined based on lifestyle. For instance, the first meal would be at 12.00 p.m. and the latest meal would be at 8:00 p.m.^{12,13}

In consideration of the results from animal trials, time restricted eating reduced body mass, total cholesterol, triglyceride, glucose, insulin, interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF- α) concentrations.¹⁴

The meta-analysis study regarding the effect of time-restricted eating on body composition and other parameters revealed that participants practicing time-restricted eating had lower body weight, fat mass while restoring lean mass, blood pressure, fasting glucose concentration, cholesterol and triglyceride.¹⁵

Ramadan Fasting

Ramadan fasting is the act of not consuming any food, beverage, medicine, cigarette, etc. in Islam for almost a month from dawn until sunset. Other than intermittent fasting, the patient is not allowed to consume any energy-free liquid or food during fasting.¹⁴

A cross-sectional study conducted with 1,780 participants with diabetes to evaluate the impact of Ramadan fasting on patients with type 2 diabetes concluded that Ramadan fasting reduces blood pressure, blood sugar, hemoglobin A1C (HbA1c), and body mass index (BMI); hence, it has a positive effect on type 2 diabetes.¹⁴

Studies have revealed that Ramadan fasting affects the loss of body weight, particularly more weight loss as BMI increases; however, people with regular weight are not affected by such circumstances. Various studies have indicated that people gain the weight that they lose during the Ramadan fasting.^{16,17}

Intermittent Fasting and Circadian Rhythm

The benefits of intermittent fasting originate from its metabolic effects, which arise from its effects on circadian rhythm. Circadian rhythm is the repetition of effects that the world has on individuals due to its 24-hour rotation like sleep-wakefulness, blood pressure, heart rate, hormone release, mood adjustment, etc. Several factors like light, melatonin, temperature, jet lag, shift work, etc. influence the circadian rhythm. The distortion of circadian rhythm may lead to many pathological events like obesity, metabolic syndrome, sleep disorders, diabetes, and cardiovascular diseases. Limiting food intake is effective in adjusting circadian rhythm.¹⁸

A large-scale randomized controlled isocaloric study covering gene expression analysis revealed that time-restricted eating affects the expression of 6 genes related to circadian rhythms. Another study noted that time-restricted eating provides significant and permanent improvement on the quality of sleep.¹⁹ Intermittent fasting may improve the quality of sleep by affecting circadian rhythms and may increase

growth hormone levels. This hormone generated while sleeping repairs the muscle cells, making one feel quite vigorous and relaxed⁽¹⁰⁾.

A one-week study performed on healthy adults concluded that individuals practicing intermittent fasting wake up and move less at night and experience an increase in REM sleep, leading to better leading better quality sleep⁽¹⁰⁾.

A study conducted via a mobile application to analyze the eating habits of a group of healthy adults showed that many individuals have frequently and irregular eating patterns, where individuals eating more than 14 hours lose body weight when they eat 10-11 hours for 16 weeks while they become much energetic with better sleep.²⁰

Intermittent fasting may improve the quality of sleep; however, there may be an opposite situation based on the practice method, particularly eating just before bedtime, which may negatively affect sleep quality. For instance, studies have concluded that waking up at night and eating during Ramadan fasting reduce melatonin levels (known as sleep hormone) and REM sleep. Moreover, leptin and ghrelin hormones affected by meal plan, food intake, sleep, etc. during Ramadan fasting may also affect circadian rhythms^{(10), 21}

Intermittent Fasting and Microbiota

Intermittent fasting may directly affect the gut biota, which comprises complex, diverse, and wide-ranging microbial groups in the gut. Karakan²² reflected that intermittent fasting encourages browning of white adipose tissue and reduces obesity by changing the gut microbiota.

Fecal samples were collected, and genomic DNA sequencing was performed within the scope of a 7-month animal study conducted with alternative day fasting. The data noted that the composition of gut microbiota and the phyla *Bacteroidetes*, *Firmicutes*, *Verrucomicrobia*, *Tenericutes*, *Actinobacteria*, and *Proteobacteria* may change with long-term intermittent fasting.²³ A study on 17 pre-diabetes patients regarding the effect of long-term fasting on the microbiota compared pre- and post-Ramadan stool and indicated an increase in *Eubacterium hallii*, *Firmucutes* bacteria.²⁴

Moreover, the consumption of fermented foods such as yoghurt, matured cheese, kefir, kimchi, kambucha, and sauerkraut with probiotics; plant-origin products with probiotics like onion, leeks, asparagus, garlic, and whole-wheat food; lentils, beans, nuts, and quinoa with high fiber and protein; and avoiding processed foods (fizzy drinks, cereals, hot-dogs etc.) would have a positive effect on gut microbiota as well as support during intermittent fasting. However, it is important to note that the gut microbiome is unique to individuals, and each person has a different reaction to food⁽¹⁰⁾.

⁽¹⁰⁾<https://www.sleepfoundation.org/physical-health/intermittent-fasting-sleep>

⁽¹⁰⁾<https://joinezoe.com/learn/intermittent-fasting-gut-health> (E.T.09.09.2022)

Intermittent Fasting and COVID-19

People continue to live amid the COVID-19 pandemic around the world. Many diseases like obesity, cardiovascular diseases, diabetes, and cancer, increase the morbidity and mortality of COVID-19. Hyperglycemia, weak immunity, inflammation, and metabolic dysfunction in obese individuals with diabetes cause severe COVID-19 symptoms.²⁵

The strategies like lockdown during the peak of cases triggered unhealthy eating habits and a sedentary life. Intermittent fasting is considered to have an impact on COVID-19 because it prevents unhealthy eating habits, improves metabolic health and immunity, reduces inflammation, and has further effects on autophagia.¹⁸

Intermittent Fasting and Obesity

Intermittent fasting is considered an effective method with various benefits against obesity. A systematic compilation study analyzing intermittent fasting and energy-restricted nutrition models for periods ranging from 14 to 48 weeks revealed that both models have similar effects on weight loss; hence, intermittent fasting may be effective in the treatment of obesity.²⁶

In addition to decreasing weight gain, intermittent fasting minimizes visceral adiposity, cardiometabolic risk, metabolism, muscle function, and glucose homeostasis.²³

Various studies have noted that intermittent fasting ensures weight loss mainly from fat.²⁷⁻²⁹ A study conducted with obese individuals in which individuals practicing 8-hour time-restricted eating for 12 weeks and individuals practicing 6-hour time-restricted eating for 8 weeks were compared with the control group observed that the intervention group had higher weight loss levels than the control group.³⁰ A clinical study on obese abdominal participants concluded that 40 participants lost around 5.3 ± 3.1 cm from their waistlines after a 3-month TRF intervention.

The meta-analysis study by Park et al.³¹ reflected that alternative day fasting minimizes BMI, body weight, and total cholesterol in overweight and obese adults.

When combined with physical activity, intermittent fasting has a greater effect on weight loss.¹⁷

Intermittent Fasting and Heart Health

Intermittent fasting limits many risk factors associated with cardiovascular diseases and consequently the occurrence of cardiovascular diseases. It reduces the concentration of inflammatory markers like IL-6, homocysteine and C-reactive protein (CRP) help the development of atherosclerotic plaque. It prevents the occurrence of heart diseases by reducing blood sugar, triglyceride, LDL levels, insulin resistance.³²

A study regarding the effect of intermittent fasting on coronary heart disease performed for 12 weeks in 32 individuals revealed that body weight and stored fat decreased but no change in lean mass was observed among participants practicing alternative day fasting.³³

Pursuant to the results of a study conducted with 60 overweight and obese adult participants, the group practicing alternative day fasting by limiting 75% of calories had lower LDL and triglyceride levels by $10 \pm 4\%$ and $17 \pm 5\%$, respectively, at the end of 12 weeks.³⁴ Similarly, a study of 83 obese individuals concluded that high-density lipoprotein and LDL levels improved with alternative day fasting and exercise.⁶

Clinical trials have indicated that intermittent fasting lowers systolic and diastolic blood pressure. A study with pre-diabetic male participants reported that an 18 h fast lowers diastolic blood pressure by 11 ± 4 mmHg and 10 ± 4 mmHg at the end of 5 weeks.³⁵

Intermittent Fasting and Insulin Resistance

During fasting, insulin sensitivity increases and insulin levels decrease, leading to the recovery of fasting and postprandial glucose levels. Insulin resistance is associated with increased CRP, lower adiponectin, LDL particle size, atherosclerosis, and increased inflammatory events with other metabolic factors that contribute to or are related to the development of coronary artery disease.³⁶

A comprehensive randomized controlled study was conducted to assess fasting glucose, insulin, HbA1c, and HOMA-IR levels to identify the effect of intermittent fasting on glucose metabolism. Consequently, the fasting glucose level decreased by 0.15 mmol/L after intermittent fasting. Glycated hemoglobin level decreased by 0.08%, but no significant change was observed in HbA1c levels. While the insulin level decreased by approximately 13.25 mU/L, the HOMA-IR decreased by 0.31.³⁷

A study regarding the effect of alternative day fasting on calorie restriction, body weight, and glycoregulatory factors in obese adults with insulin resistance revealed that the net energy intake of participants practicing alternative day fasting and a calorie-restricted diet for 6 months was reduced by approximately 25% daily. Participants following alternative day fasting consumed 25% of their daily energy needs on fasting days as lunch (between, 12.00-14.00), while they consumed 25% of their daily energy need in 3 meals while participants following a calorie-restricted diet consumed around 75% of their energy needs in 3 meals during the day. The participants were asked to restore their existing weights until the end of 12 months. At the end of 12 months, the fasting glucose of participants who practiced intermittent fasting had a higher decrease, whereas insulin resistance decreased more than that of individuals who practiced calorie-restricted diet. The decrease in body weight was similar between the groups. These findings indicate that intermittent fasting is much more beneficial than a calorie-restricted diet in reducing insulin resistance among adults with diabetes risk.³⁰

Intermittent Fasting and Brain Health

The liver is where glucose is stored as glycogen. Based on the physical activity levels of individuals, a 12-24 h fasting reduces serum glucose levels by approximately 20% or more, causing glycogen exhaustion in the liver. Because glycogen runs out during fasting, the liver transforms free fatty acids into ketone bodies and uses them as energy sources. Many tissues use fatty acids for energy, whereas while in long-term fasting, the brain uses glucose together with beta (β)-hydroxybutyrate and acetoacetate as ketone bodies. These ketone bodies stimulate brain-derived neurotrophic factor that is effective in the formation and repair of brain nerve cells. Moreover, mouse clinical trials have revealed that people practicing intermittent fasting exhibit fewer symptoms of neurodegenerative diseases (Alzheimer, Parkinson, Huntington).^{1,38}

Although the root of Alzheimer disease is not yet known, the disease is characterized by beta-amyloid plaques and neurofibrillary tangles. Intermittent fasting may diminish amyloid plaque accumulation and slow cognitive decline.³⁹

A 2-week study conducted with 90 adults between the ages of 18 and 65 identified depression symptoms in 63.2% of females (n=57) and 30.3% of males (n=33), reflecting the anxiety among individuals about losing weight.⁴⁰ In contrast to this study, a study performed for 8 weeks with 36 health volunteers concluded that intermittent fasting remedies the

headspace of participants, as measured by the Hospital Anxiety and Depression Scale and World Health Organization Well-Being Index.⁴¹

Consequently, there is not sufficient data on the direct effects of intermittent fasting on the mechanisms that support the development of brain-related diseases in humans. Therefore, there is a need for further studies.

Intermittent Fasting and Cancer

The effects of intermittent fasting on the prevalence and prognosis of cancer are not certainly known due to the lack of clinical studies. Some studies have indicated that long-term fasting may diminish chemotherapy-related toxicity and tumor growth. However, further studies are required to recommend intermittent fasting for active cancer patients.⁴²

There is not any human clinical trials on the effect of intermittent fasting on cancer, yet it is considered to have the potential to prevent cancer by decreasing DNA damage and carcinogenesis due to its impact on insulin like growth factor (IGF-1), insulin, glucose, insulin like growth factor binding protein 1, and ketone bodies.³⁸

Some studies on animals have noted that intermittent fasting may stop cancer development and progression. A mouse clinical trial concluded that individuals following intermittent fasting have 40-80% less breast tumor formation than those following ad libitum feeding.⁴³

Intermittent Fasting and Metabolic Health

Intermittent fasting may provide many metabolic benefits like the treatment of glucose homeostasis, in addition to helping to lose body fat and weight.

A study, which was conducted to identify the benefits of intermittent fasting other than weight loss, concluded that a 6-hour restricted nutrition model in males with pre-diabetes for 5 weeks improved insulin levels and sensitivity, beta cell response, blood pressure, and oxidative stress levels. Time-restricted eating as an intermittent fasting method with an effect on the harmony of eating by circadian rhythm is considered to be effective against pre-diabetes and pre-hypertension.³⁵

A meta-analysis study was performed with 335 participants with the aim of evaluating the effects of intermittent fasting and calorie-restricted diet on glycemic control and weight loss among pre-obese or obese patients and patients with type 2 diabetes and metabolic syndrome. This study revealed that intermittent fasting and a calorie-restricted diet had similar effects on glycemic control based on HbA1c and fasting plasma glucose levels. The patients experienced similar hypoglycemic events in both diet models, with improvements in fasting insulin and lipid profile. However, intermittent fasting was associated with greater weight loss.⁴⁴

Metabolic syndrome is a clinical state related to advanced cardiovascular disease and diabetes mellitus risk. Metabolic syndrome is also defined as the collective existence of risk factors, such as obesity, high fasting plasma glucose, dyslipidemia, and high blood pressure.

In consideration of the literature review, there is not any study on the direct effect of intermittent fasting on metabolic syndrome, but scientific evidence regarding the improvement of cardiometabolic parameters indicates a possible effect.¹⁵

Intermittent Fasting and Inflammation

With the development of glucose homeostasis, some studies have reported that inflammatory cytokines decrease with intermittent fasting. Moreover, TNF- α , IL-1 β , and IL-6 levels in the circulation system decrease, and weight loss and glucose metabolism are improved.^{45,46}

Similarly, intermittent fasting in rodents showed significant decreases in the circulation and fat tissue levels of IL-6, TNF- α and IGF-1 and leptin compared with ad libitum feeding mice.⁴⁷

Fasting and intermittent fasting methods reduce leptin levels and eliminate any immunity disorders related to leptin disorders, including aging, obesity, metabolic syndrome, and auto immunity.⁴⁸

A study conducted on mice with chronic inflammatory disease revealed that alternative day fasting reduced proinflammatory monocyte levels and expression of TNF- α , IL-1 β as proinflammatory genes.²⁵

Intermittent Fasting and Aging

There are several positive effects of intermittent fasting on the delay of aging, such as decreasing oxidative stress and inflammation, stimulating autophagy and inhibiting mTOR (the mammalian target of rapamycin protein complex) and decreasing insulin and glucose levels in the circulation and insulin-like growth factor.⁴⁹ Studies performed on rodents to analyze the impact of fasting on rodents indicated that the life expectancy of mice that practice alternative fasting for two days weekly is increased. Studies have shown that intermittent fasting is effective in preventing aging and age-related diseases.^{1,49} More human studies are needed to examine its effects on aging.

A randomized 4-day study conducted with 11 pre-obese adults where one group had time-restricted eating between 8 a.m. and 2 p.m. and the control group had a normal eating regime between 8 a.m. and 8 p.m. revealed that the time-restricted eating group showed a decrease in glucose levels and oxidative stress with an increase in LC3A as an autophagy gene and SIRT1 as an aging gene.⁵⁰

CONCLUSION

In particular, with an effect on weight loss, intermittent fasting has positive effects on the cardiovascular system, decreases inflammation, strengthens immunity, protects brain health, improves sleep quality, delays aging, and has potential effects on the elimination of insulin resistance and prevention of cancer. Such effects are mainly caused by the decrease in insulin levels, formation of ketone bodies, stimulation of autophagy, and decrease in oxidative stress with effects on circadian rhythm and gut microbiota. Although intermittent fasting improves many biochemicals, not everyone experiences the same benefit, and individual factors such as age, gender, and current health status may play an important role. Intermittent fasting is a type of nutrition that should be adopted as a lifestyle rather than a diet model. However, this may not be applicable to everyone because nutrition should be unique to each individual based on their needs. Intermittent fasting is not recommended during adolescence, including infancy and puberty, pregnancy, and breast feeding, for underweight individuals or individuals with eating disorders since they require more energy and nutrients. During such periods, the weight should be kept under control and sufficient protein, quality carbohydrates, healthy fat, and fruits and vegetables should be consumed based on the individual needs. In this case, it would be appropriate for the person to consult an expert and

obtain appropriate advice for their current situation. Sustainability is the key to diet modification. Intermittent fasting should be stopped when the menstrual cycle stops or becomes irregular; difficulties in sleeping occur; one starts experiencing hair loss, dry skin, and acne; any delays in wound recovery; stress; and negative effects on mental status. Many studies on intermittent fasting cover the short period; hence, a much wider scope clinical study is required to assess its long-term effects.

MAIN POINTS

- The mechanism of action of intermittent fasting is the reduction of insulin levels, formation of ketone bodies, stimulation of autophagy, reduction of oxidative stress, and circadian rhythm.
- Intermittent fasting has been shown to promote weight loss, reduce insulin resistance, and positively change leptin and adiponectin levels.
- Preclinical and clinical studies have shown that intermittent fasting has a wide range of benefits for improving cardiovascular risk factors and many diseases, including obesity, T2DM, and hypertension.

ETHICS

Authorship Contributions

Concept: S.Ç.S., Design: S.Ç.S., Literature Search: S.Ç.S., S.N.T., Writing: S.Ç.S., S.N.T.

DISCLOSURES

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