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Intermittent Fasting and Its Health Implications: A Systematic Review of Existing Research

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Abstract
Intermittent fasting (IF) strategy, including time-restricted eating (TRE), alternate day fasting (ADF), and other variations, is a dietary approach that alternates between periods of eating and fasting. This review investigates the influence of IF on human health, focusing on metabolic effects, cardiometabolic health, neurocognitive functions, and hormonal changes. IF is believed to help in weight reduction, improve insulin sensitivity, and reduce the risk of type II diabetes mellitus. It may also have positive impact on cardiovascular health by reducing blood pressure and improving lipid profiles. Moreover, IF is believed to have neuroprotective effects, improve cognitive functions and slow the progression of neurodegenerative diseases. Hormonal changes during IF are very complex and require careful management in conditions like hypothyroidism and Cushing's syndrome. Despite promising results, more research is needed to fully explore the potential negative outcomes and safety of IF. Choice of exact dietary protocol should be individualized and supervised by a healthcare provider.

Keywords: Intermittent fasting; Time-restricted eating; Alternate day fasting; Metabolic effects; Cardiometabolic health; Hormonal changes

Introduction

Intermittent Fasting (IF), time-restricted eating (TRE), and other protocols that involve eating by the clock are nutrition systems based on alternating cycles of eating and fasting.[1] While these approaches have gained popularity in recent years, their origins can be traced back to ancient times, when people naturally fasted due to food limitation or for religious reasons.[1] Although research on IF began in the 20th century, it has only gained widespread popularity in recent years. Today, it is widely recommended due to its health benefits and its ease of implementation.

Recent studies highlight multiple health benefits of implementing Intermittent Fasting (IF) as a dietary protocol. It is suggested that IF aids in body weight reduction by regulating glucose and insulin levels and increasing the body's sensitivity to insulin. In this mechanism IF reduces the risk of Type 2 Diabetes and obesity.[2] [3]

Adopting IF also lowers the risk of cardiometabolic diseases by reducing blood pressure and cholesterol levels.[3][4] Moreover, it has neuroprotective effects, supports cognitive functions, and may slow the progression or reduce the risk of neurodegenerative diseases such as Alzheimer's disease, Multiple Sclerosis, and Parkinson's disease.[4][5][6][7]Additionally, IF influences hormone levels, including estradiol, SHBG, and testosterone.[8][9]
The aim of this study is to provide a brief introduction to the concept and various models of intermittent fasting, and to analyze its impact on human health in light of the most recent medical research.

Methods

We widely and comprehensively analyzed available studies and reviews found in research on PubMed, Google Scholar and Scopus. We used following search terms: „intermittent fasting", „alternate day fasting", „time-restricted fasting", „fasting" We focus on human studies, but also present compelling evidence from rodent models. We included following types of studies: meta-analyzes, randomized controlled trials, cross-over studies, case studies, and observational studies. There were no limitations on publication date or language. Articles were screened based on titles and abstracts, and duplicates were removed. Full-text reviews were conducted for relevant studies. Studies were categorized based on outcomes related to metabolic effects, cardiovascular health, neurocognitive functions and hormonal changes.

Various models of intermittent fasting

There are several variations of intermittent fasting, including:

1. **Time-Restricted Eating (TRE) / Time-Restricted Feeding (TRF)** – This is the most commonly used type, where there is an 8-hour "eating window" followed by 16 hours of fasting. It is a relatively simple, easy-to-maintain, and well-tolerated method.[1][10]
2. **Twice-Per-Week Fasting (TWF)** – This method involves normal nutrition for five days per week, with two calorie-restricted days limited to 500-600 kcal per day.[10]
3. **Alternate Day Fasting (ADF)** – This type involves alternating fasting days with regular eating days. On fasting days, calorie consumption is restricted to 500-600 kcal per day or may be completely forbidden. While this method provides quick results, it is very difficult to follow as a long-term dietary approach.[1][10]
4. **Eat-Stop-Eat** – This approach involves complete fasting for 24 hours once or twice a week. It often causes several side effects, such as loss of concentration and fatigue.

Choosing the best method should depend on the patient's individual preferences and health conditions.[11] The most balanced and easiest-to-maintain regimen is the TRE method, with an 8-hour eating window. In clinical practice, ADF is also a widely used approach, but it can lead to multiple side effects, such as hormonal disturbances in women, lack of energy and fatigue, hunger attacks, and overeating after the fasting period ends.[11]

Metabolic effects of IF

Recent studies suggest that intermittent fasting can positively affect carbohydrate metabolism, which is crucial in the prevention and treatment of type II diabetes mellitus and obesity.[2] This dietary protocol supports weight reduction [4], primarily by reducing fat mass while preserving lean body mass. It also lowers fasting blood glucose and insulin levels, leading to an improved HOMA-IR index and HbA1c.[12] Additionally, periodic fasting enhances tissue responsiveness to insulin.[3]

However, it is important to consider that the effects depend on the specific fasting model. For example, the ADF model has shown the most promising results in weight loss and reduction of inflammation markers but carries the highest risk of hypoglycemia. [13] On the other hand, the TRE model has also demonstrated satisfactory results and is easier to implement and maintain.[11]

A review of studies published in *Nutrients* highlights that both ADF and TRE can effectively support weight loss and improve metabolic markers. However, their effectiveness may depend on individual preferences and the ability to maintain the diet long-term.[11]

Despite these promising results, more long-term studies are needed to thoroughly analyze potential negative health outcomes associated with prolonged intermittent fasting in patients with type II DM and obesity.

Cardiometabolic health influence

Intermittent Fasting has a broad impact on cardiomethabolic health. The potentially positive cardiometabolic effects of intermittent fasting may stem from its overall impact on weight reduction, although some studies suggest that it can be beneficial even without weight loss. First of all many studies prove that this dietary protocol can reduce systolic and diastolic blood pressure[4] [10] What's more this antihypertensive impact can remain below the pre-fasting levels for few weeks to few months even after introducing food, but it also depends on post-fasting nutritional and lifestyle habits.[14-19]

Secondly, most studies revealed positive outcomes of if in lipid profile, including decreasing LDL-C [14] [17] [19-22] and triglicedydes [15] [17] [19-23] levels and in some cases increasing HDL level. [3] The best positive outcome was observed during TRE model of IF. [3]

Some studies also reported a substantial decrease in oxidative stress. [19], aPTT, PT and fibrynogen levels.

Considering the effects described above, it can be concluded that IF lowers the risk of coronary artery disease. [24-25]. Furthermore ADF is known to reduce apoptosis level in the peri-infarct area in experimental ischemia [26-27]

Hormonal changes in IF

Several studies have demonstrated significant hormonal changes during periodic fasting.

Thyroid hormones

Rodent studies have shown that fasting enhances the activation of deiodinase III, which inactivates thyroid hormones, leading to lower T3 levels. Interestingly, unlike primary hypothyroidism, fasting does not compensatorily increase TSH and TRH levels but instead decreases them. This may be due to changes in leptin and neuromedin B levels during fasting. A reduction in T3 levels during fasting has also been observed in human studies, whereas TSH levels remain unchanged in both ADF and TRF fasting models.

Given these changes, hypothyroid patients following intermittent fasting (IF) may require higher doses of levothyroxine and should remain under medical supervision while on such a diet. [28]

Cortisol levels

Periodic calorie restriction is suggested to be a physical stress factor, which is reflected in changes in cortisol levels. Even a few days of fasting can increase cortisol levels and shift peak secretion from the morning to the afternoon.

These changes should be taken into consideration in patients with Cushing's syndrome and hypercortisolism.

Estradiol

There are very few studies investigating the influence of intermittent fasting (IF) on estradiol levels. One of them, conducted by Jakubowicz et al. [29], found that women who consumed more than 50% of their daily caloric intake at breakfast had lower estradiol levels after 12 weeks compared to those who consumed more than 50% of their calories at dinner. This strategy may be worth considering for premenopausal PCOS patients to prevent further increases in estrogen levels. However, in contrast, a study on mice revealed that the alternate-day fasting (ADF) model led to an abnormally increased estradiol level and a significant decrease in luteinizing hormone [30], which disrupted the reproductive cycle. This effect was not observed in the time-restricted feeding (TRF) model; on the contrary, TRF appeared to improve reproductive function. [31-32]

SHBG and Androgens

The effect of periodic calorie restriction on SHBG and androgens has been studied in three experiments in females. All suggested that IF increases SHBG levels, even without changes in body weight, while lowering DHEA-S and testosterone levels. These findings may be crucial for women with PCOS experiencing hyperandrogenism symptoms, such as hirsutism, seborrheic acne, and others. [29] [33-34]

In all studies conducted on men, time-restricted eating (TRE) reduced free testosterone levels, regardless of whether it was implemented alone or combined with resistance training. Simultaneously SHBG levels remained unchanged. [8] Interestingly these changes did not lead to detrimental changes in body composition or loss of muscular strength.

Other hormones

In most studies, the IF regimen did not affect FSH or LH levels, even after weight reduction. It also had no impact on prolactin and was therefore considered safe for breastfeeding women.[9][8]

Neurological effects of IF

Recent studies have revealed that metabolic changes during fasting may enhance brain function by increasing neuroplasticity, improving cognitive performance, and boosting resistance to injury. During intermittent fasting (IF), most of the brain's energy comes from ketones, primarily beta-hydroxybutyrate (BHB). This enhances the production of brain-derived neurotrophic factor (BDNF), which supports neuronal survival, promotes neurogenesis in the hippocampus, improves learning and memory, strengthens synaptic function, and reduces neuroinflammation. [35-39]

The IF regimen also increases PGC-1α expression, which is associated with improved cognitive function and spatial memory, while also enhancing BDNF expression. Moreover, IF inhibits the mTOR pathway, which is overactivated in epilepsy, multiple sclerosis, and Parkinson's disease. As a result, such a dietary intervention could potentially offer protective effects against the development of these disorders. [40-45].

Another study shows that IF can influence post-stroke brain damage. Mice subjected to IF for 4–5 months before the induced stroke exhibited lower levels of brain damage, likely due to fasting-dependent increases in FGF-2 levels and its protective effects. [46]

Furthermore, intermittent food deprivation also increases GABA levels, facilitating adaptive responses, as well as the levels of neurotrophic factors such as IGF-1 and ghrelin. The last one stimulates serotonin neurons in the hippocampus, enhances neuronal survival, and influences neuroplasticity. [7]

Considering all mentioned metabolic mechanisms intermittent fasting may have important role in neurometabolic diseases. It is known that IF reduces Beta-amyloid accumulation and cognitive function in Alzheimer's disease. Animal studies suggest that IF delays CNS degeneration by protecting dopaminergic neurons in Parkinsons disease. IT also modulates immune response in multiple sclerosis, by affecting gut microbiome, reduces peri-infarct brain damage in mice and improve neurotransmission and stress resilience in depression. However, in some patients with affective disorders, it may lead to a worsening of symptoms, especially in cases of schizophrenia or bipolar disorder.

Conclusions

Intermittent fasting is a comprehensive dietary approach with a wide range of potential health benefits. It is a valuable tool in holistic care of patients with obesity and DM type II, due to its metabolic effects, such as improved insulin sensitivity and weight loss. It has clear positive impact on cardiovascular health through the lowering of blood pressure and improvement in lipid profiles, thus reducing the risk of coronary artery disease.

Moreover, IF may be beneficial in conditions like Alzheimer's disease, Parkinson's disease, and multiple sclerosis. It has significant implications for neurocognitive health, with potential neuroprotective effects and the ability to boost cognitive performance.

Varied and complex hormonal changes caused by IF can be beneficial in certain conditions like PCOS, but require careful management in others, such as hypothyroidism or Cushing's syndrome.

However, the choice of specific IF protocols must be individualized, taking into account the patient's preferences, lifestyle, and unique health conditions.[11] While the findings are encouraging, these results call for more extensive and long-term research to fully assess the potential negative health outcomes and to optimize the use of IF in different medical contexts. It's important to be aware that IF is not suitable for everyone, and it should be practices under the medical supervision, especially for individuals with specific health conditions or those on specific medications. Nevertheless, IF remains a promising area of nutritional science with significant potential to enhance public health.

Discussion

Intermittent fasting (IF) is a promising nutritional strategy that offers multiple health benefits, including body weight reduction, improved carbohydrate metabolism, and potential protective effects against various chronic diseases. As highlighted in this study, recent researches suggest that IF may also positively influence metabolic health, as well as the circulatory, nervous, and hormonal systems. Despite these promising findings, many of the analyzed scientific studies still have significant limitations.

One of the main issues is the insufficient number of long-term studies conducted on humans. Most recent research has been short-term and based on small study groups, which limits its scientific value and the ability to generalize the results. Additionally, many studies have focused on healthy individuals or overweight patients, leaving a gap in solid evidence regarding the effectiveness and safety of IF for patients with various medical conditions. Furthermore, some studies were conducted exclusively on rodents, making it necessary to assess whether the observed effects can be replicated in human trials.

Another key concern is the need for more studies comparing IF protocols with traditional calorie restriction models. It remains unclear whether the benefits of IF stem from the fasting window itself or simply from reduced overall calorie intake and weight loss. The quality of the diet followed during IF may also play a crucial role-it is uncertain whether the observed effects result from the fasting structure alone or from an overall improvement in dietary habits.

Despite these limitations, intermittent fasting remains an exciting and rapidly evolving area of nutritional research. If future studies confirm its effectiveness and safety across diverse populations, IF could become a valuable tool in promoting public health and combating diet-related diseases.

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