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Physiology of intermittent fasting

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Abstract
There is a continuing need for new and efficient weight-control methods due to the long-lasting consequences of the obesity pandemic on public health outcomes. Intermittent fasting, which comprises a variety of timing regimens for temporary food avoidance, such as alternate-day fasting, alternative full-day fasting patterns, and time-restricted feeding, is one strategy for enhancing weight and metabolic outcomes. The irregular conversion of fatty acids into ketones encouraged by these diets has positive metabolic consequences. The programmes generally support weight loss and have been associated with reduced blood pressure and dyslipidaemia. Intermittent fasting should be taken into consideration as a possibility for people who have a tendency to gain weight unhealthily using conventional eating habits, even if more research is needed on the long-term implications and this strategy should be avoided in particular health conditions.

Keywords: Intermittent fasting, physiology, circadian rhythm, metabolic switching, autophagy

Introduction
Because obesity [1] and the metabolic syndrome (MetS) are becoming increasingly commonplace globally, the medical community is working harder to create novel treatments to counteract their pathophysiological effects. Although significant progress has been made in developing new medical treatments for obesity, there has recently been a rise in interest in changing eating patterns through various dietary regimens. Intermittent fasting is one such method that has consistently been recommended by health professionals due to its benefits for oxidative stress, cardiovascular health, and weight control. One of the oldest traditions in the world, fasting has been practised for both cultural and religious reasons by a wide range of people. It's noteworthy to note that it was once used to treat ailments as well. The saying "To eat when you are sick is to feed your ailment" was reportedly penned by Hippocrates, the founder of modern medicine. According to Philip Paracelsus, the father of toxicology and one of the three architects of contemporary Western medicine together with Hippocrates and Galen, fasting is the best cure—the inner doctor. According to American founding father Benjamin Franklin, rest and fasting are the best treatments (1706-1790). Finally, for spiritual reasons, fasting is still practised by virtually all major religions.

Intermittent Fasting
Intermittent fasting (IF) is a catch-all name for a variety of dietary practises that alternate between periods of not fasting and periods of total fasting or severe caloric restriction (whether long or short).

Intermittent fasting strategies [3]
1. **When eating, use the 16/8 or 14/10 rule: You can decide to do this and establish times for eating and fasting. If you fast for 16 hours, for example, you might only be able to eat for 8 of those hours**
- The "16/8" approach, which prohibits eating after 8 o'clock.
- On the "14/10" diet, eat only between 9 a.m. and 7 p.m.

2. **A frequency of twice weekly (the 5:2 method):** This particular style of intermittent fasting emphasises the need of eating no more than 500 calories on two days each week. You consume a typical, wholesome diet the other five days of the week.
3. **Switching between days of fasting:** A "modified" fast is observed every other day in this way. Keep your daily calorie intake to 500, or roughly 25% of your normal intake, on days when you fast. You should resume your regular, healthy diet on days when you are not fasting.

4. **The one-day fast (or eat: stop: eat method):** For this approach, a strict 24-hour fast is necessary. Only occasionally—once or twice a week—does it occur.

It has been proposed in the literature that the natural circadian rhythm [4] is the main mechanism in charge of maintaining a metabolic balance. The 24-hour balance of anabolic and catabolic activity is mostly regulated by the circadian rhythm. The daily fed-fast cyclical rhythm is required to maintain the balance between mRNA and proteins, which controls various aspects of metabolism including glycolysis, protein synthesis, lipid synthesis and oxidation, gluconeogenesis, and mitochondrial activities. It follows that anytime there is a discrepancy between circadian timing and daily food intake patterns, this may result in a disruption of the circadian rhythm, which may then have an adverse impact on the metabolic system. Examples include heightened insulin resistance, higher oxidative stress, and impaired hormone secretion.

The significance of intermittent fasting in maintaining a healthy circadian rhythm, which in turn regulates metabolic processes, has been demonstrated by a few studies using mice as a model. Intermittent fasting, which involves a routine of time-restricted eating to lessen circadian rhythm disruption and ultimately improve metabolic balance, enables a constant duration of fasting each day. Mice's gut organ systems, brown adipose tissue, and white adipose tissue have all been proven to benefit from time-restricted eating, as have insects (brain, heart, and muscle). Furthermore, in animal models, time-restricted eating prevented fatty liver, dyslipidaemia, and glucose intolerance.

Recent small-scale research on humans have shown the importance of a time-restricted feeding routine in maintaining a healthy metabolism. Most of these studies supported the notion that intermittent fasting has similar beneficial effects on a variety of aspects of human metabolism as those observed in animal studies. The effects of time-restricted eating were decreased calorie intake, body weight, body fat, blood pressure, blood sugar, TG, glucose tolerance, and inflammatory markers.

Physiology of Intermittent Fasting

When discussing intermittent fasting and its effects on health, it is essential to know the basic physiology of glucose and lipid metabolism as well as the concept of "metabolic switching" [5] that occurs during the fasting state. Randle and colleagues proposed the "glucose-fatty acid cycle" in 1963 [6] to explain how glucose and fatty acids compete for oxidation during feeding and fasting. The fed-fast cycle consists of four phases: fed, post-absorptive, early fasting, fasting, and starvation, or long-term fast. Glucose serves as the majority of tissues' primary source of energy throughout the day. Following meals, glucose is converted to triglycerides in adipose tissue and used as fuel. During extended fasting intervals, triglycerides from adipose tissue are converted to fatty acids and glycerol and used as fuel. Fats are then converted by the liver into ketone bodies, which during a fast serve as a vital source of energy for several tissues, including the brain. The only stages that are relevant to daily eating habits are the feeding and post-absorptive ones. When adopting an intermittent fasting diet, a person frequently alternates between the fed, post-absorptive, and fasting periods. Insulin is the primary driving hormone when the body is fed, using glucose as fuel, whereas glucagon is the primary driving hormone when the body is fasting, burning liver glycogen reserves as fuel. The metabolic shift starts at the point of negative energy balance where liver glycogen reserves are depleted and fatty acids are metabolised. This typically occurs more than 12 hours after the previous meal. The evolutionary trigger that causes the metabolic shift from using glucose to fatty acid-derived ketones shifts metabolism away from lipid/cholesterol synthesis and fat storage and towards the mobilisation of fat through fatty acid oxidation and fatty-acid derived ketones is the metabolic switch from using glucose to fatty acid-derived ketones. This helps to preserve muscle mass and function. It has therefore been suggested that intermittent fasting regimens that cause this metabolic change may benefit obese patients by improving their body composition.

There are numerous routes that result in improved metabolism, a longer life span, and metabolic switching during intermittent fasting. Rising AMP (and ADP) and declining cellular ATP activate AMP-activated protein kinase (AMPK), which ultimately inhibits a number of anabolic pathways and encourages catabolic responses like autophagy. By eliminating damaged proteins and organelles, autophagy [7] aids mitochondrial function. Because lower levels of circulating glucose and amino acids block mTOR, which in turn results in higher levels of autophagy and mitochondrial biogenesis, experimental animals live longer as a result [8]. In addition to mobilising fatty acids from adipose tissues and promoting hepatic -oxidation with an increase in ketone production, fasting depletes liver glycogen by reducing carbohydrate consumption (beta hydroxybutyrate). Additionally, the NAD+ deacetylase activity of sirtuins [9] is enhanced, which supports autophagy and reduces oxidative stress. Together, these routes lengthen lives and advance health.

By activating the transcription factors peroxisome proliferator-activated receptor (PPAR-) and activating transcription factor 4 (ATF-4), free fatty acids also result in the production and circulation of fibroblast growth factor 21 (10) (FGF21), a protein with significant effects on various cell types throughout the body and brain (ATF4). Additionally, beta hydroxybutyrate has signalling features that include BDNF production in neurons and the activation of transcription factors including cyclic AMP response element-binding protein (CREB) and nuclear factor b (NF-B).

Advantages of intermittent fasting

Intermittent fasting causes the body to transition from using glucose-based energy to ketone-based energy, extending life expectancy, lowering the risk of diseases like cancer and obesity, and boosting stress tolerance. Intermittent fasting has shown positive effects on weight loss in addition to reducing insulin resistance and favourably altering the levels of leptin and adiponectin [11]. Pre-clinical and clinical investigations have demonstrated that intermittent fasting provides a wide range of benefits for numerous illnesses, including obesity, type 2 diabetes, and hypertension, as well as for lowering cardiovascular risk factors. A surprising impact of IF on the composition of the gut microbiota is the enrichment of the Bacteroide, Lactobacillus, and Proteaceae groups [12]. The amount of lactobacilli produced by intermittent fasting was particularly noteworthy because it is

commonly used as a probiotic due to its positive effects, which include a decrease in the inflammatory immune response.

Reason for Caution with Intermittent Fasting

Although intermittent fasting provides advantages, there are also some disadvantages. The short time frames employed to examine intermittent fasting regimens are mostly to blame for the paucity of data demonstrating their harmful effects (weeks to months). Weakness, vertigo, and hypoglycaemia are a some of the frequently mentioned adverse effects. Fasting without adequate protein replacement is also known to encourage muscular atrophy, thus it should be avoided. Hormonal disorders, pregnancy, breastfeeding, young children, the elderly, and individuals with immune weaknesses—in particular, those with a history of solid organ donation and subsequent medical immunosuppression—are contraindications to fasting. Scheduled fasting may exacerbate problems already experienced by those with dementia or eating disorders; for this reason, intermittent fasting schedules should be avoided.

Conclusions

Even a short fasting period (like overnight) in humans can reduce basal levels of many metabolic markers linked to chronic disease, such as insulin and glucose. For example, patients must fast for 8 to 12 hours before taking blood samples to get steady state fasting levels of a number of metabolic substrates and hormones. A key clinical and scientific problem is whether implementing a regular, intermittent fasting schedule is a practical and long-term population-based strategy for enhancing metabolic health. This review suggests that intermittent fasting regimens may be an effective way to lose weight and improve metabolic health for people who can tolerate periods of not eating, or eating very little, for particular hours of the day, night, or days of the week. These diet plans may provide promising non-pharmacological strategies for improving population health, which could have a wide range of advantageous consequences on public health if they are proven to be effective.

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