Chapter

Fasting Physiological Effects

Linda Afriyie Gyimah

Abstract

Fasting is a widespread practice across cultures and religions, involving abstaining from food and sometimes specific types of food for defined periods. Fasting has evolved into a ritualistic, spiritual, and health-promoting practice. Fasting encourages the body to create ketones. These molecules act as a substitute energy source for different body parts, with the brain particularly proficient at utilizing them for energy. This cascade of metabolic adaptations involves several key organ systems: the pancreas for hormonal regulation, the liver for glycogen storage and fat metabolism, adipose tissue as an energy reserve, and skeletal muscle as a potential protein source—all working in concert to maintain energy homeostasis during periods of fasting. Fasting can positively impact various markers of health, including cardiovascular disease, cancer, and neurodegenerative diseases. While highlighting potential benefits, the review also acknowledges potential negative effects as well. This review summarizes the literature on fasting and its effects on the body.

Keywords: fasting, ketosis, gluconeogenesis, autophagy, gut microbiome, insulin sensitivity

1. Introduction

Throughout the past and across diverse societies and faiths, people have engaged in fasting. Historically, fasting has been associated with spiritual purification and religious observance [1]. In contemporary settings, fasting is also adopted for weight management, metabolic health improvements, and potential therapeutic benefits in chronic disease prevention and treatment [2]. Fasting is a means of refraining from consuming any food or beverage for a specified duration. In a broader interpretation, it may also involve avoiding particular types of food for a set period of time [3]. Fasting is the abstinence from all or some foods or drinks for a set period of time. Fasting, the voluntary abstinence from food for a period of time, induces various physiological effects in the human body. These effects may be positive or negative. Normally, most human beings engage in an unintentional overnight fast between 8 and 12 hours daily. In the early days, humans fasted inadvertently when they were not certain about the safety of foods. As human culture developed, fasting became associated with religious devotion, often performed as a sacrifice to deities. Additionally, fasting is seen as a method to purify both the physical body and the mind [4]. The physiological effects of fasting are orchestrated by complex interactions among various organ systems, hormonal signaling pathways, and metabolic adaptations. Delving into metabolic shifts, hormone regulation, and cellular repair processes, this topic sheds light on how fasting influences health, longevity, and overall well-being. As human societies progressed, fasting became associated with multiple purposes:

1. Religious devotion: Many faiths (Christianity, Islam, and Judaism) incorporate fasting as a spiritual practice or offering to deities.

2. Physical well-being: Fasting is seen as a way to cleanse and rejuvenate the body.

3. Political expression or protest: Some individuals or groups use fasting as a form of non-violent demonstration.

4. Medical reasons: Prior to surgical operations.

Different mechanisms exist to enable the storage of energy and its mobilization when fasting or during periods of starvation. The following are the mechanisms that exist during fasting based on the duration [5].

1. Fed phase (0–4 hours after eating)

Digestion of recently consumed food and absorption of its nutrients actively occur in this phase. Consequently, blood sugar concentrations increase, triggering the pancreas to secrete insulin. This hormone facilitates cellular absorption of glucose and converts surplus glucose into glycogen, which is then stored in the liver and muscle tissues. When there is a positive energy balance, that is, when caloric intake exceeds immediate energy needs, the excess calories are stored as fat.

2. Postabsorptive phase (4–18 hours)

In this phase, blood sugar begins to decline when the body has completely absorbed the nutrients from the previous meal. To keep blood glucose within a normal range, the body begins to break down glycogen stored in the liver in a process called glycogenolysis. This leads to a decrease in insulin production and a corresponding increase in the secretion of the hormone glucagon. This hormonal shift boosts the release of glucose that had been stored earlier.

3. Gluconeogenesis (18–48 hours)

After the liver's glycogen reserves are exhausted, the body shifts to manufacturing glucose from sources other than carbohydrates in a process termed gluconeogenesis. This process primarily uses amino acids obtained from breaking down proteins. Concurrently, the breakdown of fat (lipolysis) accelerates, which releases fatty acids that can be used as an energy source. This dual approach helps the body maintain its energy needs when carbohydrate sources are no longer available.

4. Ketosis (48–72 hours)

With prolonged fasting, the body substantially accelerates the process of breaking down fat. In the liver, fatty acids are transformed into compounds called ketone bodies (acetoacetate, β-hydroxybutyrate, and acetone). Ketone bodies serve as an alternative fuel source for various organs, with the brain particularly proficient at utilizing them for energy. This metabolic state, characterized by elevated ketone levels in the blood, is referred to as ketosis.

5. Protein conservation (72+ hours)

During extended periods of fasting, the body implements strategies to protect muscle tissue. The rate of protein breakdown decreases as the body adapts to this state. Simultaneously, the body's efficiency in utilizing ketones as an energy source improves. To further safeguard muscle mass, there is an increase in the production of growth hormones. These coordinated changes allow the body to maintain essential muscle tissue while relying primarily on fat-derived energy sources during prolonged fasting.

2. Classification of fasting

Fasting can be classified based on duration, frequency, and the degree of caloric restriction. Thus, fasting may be short-term or prolonged (>8 days). The following are the classifications of fasting:

1. Intermittent fasting

Intermittent fasting (IF) entails consistent, alternating periods of restraint from caloric consumption and ad libitum eating. The three intermittent fasting approaches that have received the most research attention in human studies are alternate-day fasting, the 5:2 method, and time-restricted eating [2]. These three protocols represent the most commonly investigated forms of intermittent fasting in the scientific literature. Each approach offers a different pattern of alternating between periods of normal eating and periods of caloric restriction or complete fasting.

a. Alternate-day fasting (ADF)—with ADF, individuals fast on alternating days, that is, fasting is done for 24 hours and ad libitum eating days the following day.

b. The 5:2 method—this involves fasting for two non-consecutive days per week and 5 days of normal eating.

c. Time-restricted eating—this involves daily fasting for 12–20 hours. Examples are the 16:8 diet, where the individual fasts for 16 hours and eats for 8 hours daily.

2. Religious fasting—various fasting practices are associated with different religions.

a. Christians: Christians observe a 40-day period of fasting and abstinence, excluding Sundays, modeled after Jesus Christ's 40-day fast in the wilderness before he began his public ministry. This practice, often called Lent, involves self-discipline, spiritual reflection, and abstaining from certain foods or activities as a means of spiritual preparation and renewal.

b. Ramadan fasting (Islamic): Ramadan fasting is a month-long Islamic practice where Muslims abstain from food, drink, and other physical needs from dawn to sunset. This period of daily fasting is accompanied by increased prayer, charity, and self-reflection, aiming to strengthen faith and foster spiritual growth. While exempt groups exist, most adult Muslims participate, adjusting their daily routines to accommodate pre-dawn and post-sunset meals.

c. Yom Kippur fasting (Jewish): Yom Kippur, the Day of Atonement, is the holiest day in the Jewish calendar. It involves a 25-hour complete fast from food and drink, starting before sunset on the evening before Yom Kippur and ending after nightfall the next day. This fast is observed by most adult Jews, except those whose health would be at risk. The fasting is part of a broader day of prayer, repentance, and self-reflection, aimed at spiritual cleansing and renewed commitment to Jewish faith and values.

3. Therapeutic fasting—this is used as a medical intervention, often under supervision.

   a. Water fasting: Consumption of only water for a set period, typically for detoxification or weight loss.

   b. Juice fasting: Consumption of only fruit and vegetable juices for a set period

4. Fasting-Mimicking Diets (FMD)—FMD requires strict health expert supervision. It involves the consumption of very-low-calorie diets that aim to produce similar metabolic effects as complete fasting. It typically involves five consecutive days of severe calorie restriction (800–1100 kcal/day) repeated periodically (e.g., once a month).

During fasting, multiple organ systems are affected, with the pancreas playing a primary role in the initial response. As blood glucose levels drop, the pancreas increases glucagon secretion from the alpha cells in the islets of Langerhans. This hormone primarily targets the liver, which houses the majority of the body's glycogen stores, while also affecting skeletal muscle to a lesser degree due to its lower glycogen content.

The pancreas operates independently through its connection to both the sympathetic and parasympathetic nervous systems. Additionally, various parts of the brain, such as the hypothalamus, cerebellum, and hippocampus, contain insulin receptors. These receptors are not limited to these areas but are found in other brain regions as well.

Once hepatic glycogen is depleted, the body shifts to utilizing adipose tissue and proteins for energy. The liver becomes central to fat metabolism, serving as the main site for triglyceride oxidation. In prolonged or extreme fasting situations, when fat sources are exhausted, the body resorts to breaking down skeletal muscle for energy. This process provides amino acids for metabolism but results in a decrease in muscle mass.

When we consume food, the digestive tract releases specific hormones. These gut hormones play crucial roles in regulating several physiological processes, including the following:

1. Control of appetite

2. Regulation of glucose production

3. Management of gastric emptying rates

4. Facilitation of glucose uptake from the bloodstream

These hormones act as key mediators in the body's response to nutrient intake, helping to maintain metabolic balance and energy homeostasis.

This cascade of metabolic adaptations involves several key organ systems—the pancreas for hormonal regulation, the liver for glycogen storage and fat metabolism, adipose tissue as an energy reserve, and skeletal muscle as a potential protein source—all working in concert to maintain energy homeostasis during periods of fasting [6].

3. Physiological effects of fasting

Fasting triggers a significant shift in how our cells function and how our body processes energy. This change induces various positive or negative physiological effects in the human body, which are discussed below:

3.1 Metabolic effects

Normally, when we eat, the body obtains nutrients from the food for various functions, including energy production. The body relies on glucose in the blood for energy through a process called glycolysis. However, during fasting, the body must maintain blood glucose levels differently. The human body changes from the use of glucose for energy to fat oxidation during fasting. Initially, it taps into glycogen (stored glucose) reserves located in the liver and skeletal muscles. Glycogen consists of linked glucose molecules that can be broken down for energy through glycogenolysis. The liver, which holds the largest glycogen stores, plays a crucial role in sustaining blood glucose levels during the first day of fasting. Once about 24 hours have passed, these glycogen reserves become depleted. At this point, the body shifts to using energy stored in fat tissue and protein sources to maintain its functions [7]. After glycogen stores are exhausted, a major metabolic shift occurs, primarily driven by the breakdown of fat stored in adipose tissue. This process involves the following:

a. Triglyceride breakdown: Triglycerides in fat cells are split into free fatty acids and glycerol.

b. Liver conversion: The liver transforms these components—glycerol is converted to glucose, while free fatty acids are converted to ketone bodies (β-hydroxybutyrate, acetone, and acetoacetate), a process known as ketogenesis for energy use. The production of ketones serves as an alternative energy source for the brain and other organs. The brain, which typically relies heavily on glucose, gradually adapts to use ketones for up to 60–70% of its energy needs during prolonged fasting.

c. Energy distribution: Ketone bodies circulate through the body and are converted back to acetyl-CoA in tissues needing energy.

Simultaneously, protein breakdown (catabolism) occurs through gluconeogenesis. This process creates glucose from amino acids derived from various body tissues, including muscle. This newly created glucose helps maintain blood sugar levels and provides energy for glucose-dependent tissues (like the brain, although the brain can also use ketones to some extent). These simultaneous processes demonstrate how the body adapts to maintain energy balance during fasting, using both fat and protein stores to meet its energy needs. The shift to ketone body utilization helps spare protein by reducing the need for extensive gluconeogenesis, though some protein breakdown still occurs. Mattson et al. [8] describe that this metabolic change can enhance glucose control, boost resilience to stress, and reduce inflammation. The transition to using ketone bodies is linked to elevated levels of brain-derived neurotrophic factor (BDNF), which supports cognitive function and neuroplasticity.

3.2 Insulin sensitivity

Fasting periods allow insulin levels to decrease significantly, giving cells a break from constant exposure to this hormone. This can lead to improved insulin sensitivity, meaning cells become more responsive to insulin when it is present. Additionally, fasting may increase the expression of insulin-sensitive glucose transporters (GLUT4) in muscle cells. This improved insulin sensitivity can lead to better glucose control and potentially reduce the risk of type 2 diabetes [9]. Another study [10] demonstrated that alternate-day fasting for 2 weeks increased insulin-mediated glucose uptake rates by 25%. This improvement in insulin sensitivity can have far-reaching effects, potentially reducing the risk of type 2 diabetes and other metabolic disorders.

3.3 Cardiovascular health

Fasting can positively impact various markers of cardiovascular health. Moro and colleagues [11] studied the effects of time-restricted feeding (16 hours of fasting, 8 hours of feeding) over 8 weeks. They found significant reductions in blood pressure, total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Research on intermittent fasting suggests it can significantly improve blood lipid profiles. Studies examining both alternate-day and whole-day fasting protocols, lasting from 3 to 24 weeks, have demonstrated notable reductions in various lipid markers. Participants across different weight categories experienced decreases in LDL cholesterol (20–25%), total cholesterol (5–21%), triglycerides (14–50%), and triacylglycerol concentrations (15–30%) [12, 13]. Additionally, Longo and Mattson [9] found that intermittent or periodic fasting has protective effects against diabetes, cancers, heart disease, and neurodegeneration in rodents, while human studies have alleviated obesity, hypertension, asthma, and rheumatoid arthritis. These consistent findings across multiple studies and fasting methods indicate that intermittent fasting can be an effective approach for lowering blood lipids, which may contribute to improved cardiovascular health, therefore, potentially reducing the risk of cardiovascular diseases.

3.4 Autophagy

Autophagy is a vital cellular maintenance process that utilizes lysosomes to break down and recycle various components within the cell [14]. This mechanism serves as a protective housekeeping system, targeting and eliminating damaged organelles, misfolded proteins that have outlived their usefulness, and even invading pathogens. By recycling these cellular materials, autophagy provides building blocks and energy for cellular renovation and helps maintain homeostasis. This process is crucial for cells to adapt to stress and maintain optimal function. Essentially, autophagy acts as a cellular "self-eating" system that cleans up, recycles, and renews cellular components, thereby promoting overall cellular health and resilience [14]. Enhanced autophagy has been associated with improved neuronal health, reduced inflammation, and better overall cellular function. The activation of autophagy during fasting is thought to be an evolutionary adaptation that allows organisms to recycle cellular components for energy and maintain cellular health during periods of nutrient scarcity [14]. Another study [15] also found out that short-term fasting (24–48 hours) induced a dramatic upregulation of autophagy in brain cells. This increased autophagy may contribute to the neuroprotective effects of fasting, potentially reducing the risk of neurodegenerative diseases.

3.5 Inflammation

Chronic inflammation is associated with numerous diseases, including cardiovascular disease, cancer, and neurodegenerative disorders. Fasting appears to have anti-inflammatory effects. Research [16, 17] indicates that fasting reduces markers of systemic inflammation, such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6). This anti-inflammatory effect may be mediated through several mechanisms, including the reduction of oxidative stress, modulation of the gut microbiome, and alterations in gene expression. The anti-inflammatory effects of fasting may contribute to its potential benefits for various chronic diseases. Fasting appears to increase the vulnerability of cancer cells to chemotherapy while potentially protecting healthy cells, thus reducing side effects [18]. It induces metabolic changes that counter cancer cells' typical adaptations, such as the Warburg effect, and promotes apoptosis in these cells [19, 20], which leads to an increase in oxygen consumption while decreasing adenosine triphosphate (ATP) synthesis, suggesting heightened mitochondrial uncoupling [21].

3.6 Neurological effects

Fasting shows promising neuroprotective effects, potentially enhancing cognitive function and lowering the susceptibility to neurodegenerative diseases. A study [22] demonstrated that intermittent fasting protected against age-related cognitive decline in animal models. The researchers found that fasting reduced neuroinflammation and oxidative stress in the brain, which are key factors in cognitive decline and neurodegenerative diseases.

3.7 Hormonal change

Fasting influences the secretion of various hormones. One notable effect is the increase in human growth hormone (HGH) secretion. A study [23] found that a two-day fast increased the frequency and amplitude of growth hormone secretory bursts in men. HGH plays crucial roles in metabolism, muscle growth, and cellular repair processes. According to Longo and Mattson [9], other hormonal changes during fasting include decreased insulin levels, increased glucagon levels, and increased norepinephrine levels. Insulin levels decrease rapidly, allowing for increased lipolysis and fatty acid oxidation. During fasting periods, increased secretion of glucagon stimulates processes such as glycogenolysis and gluconeogenesis, which help maintain stable blood glucose levels [24]. Growth hormone production is elevated, which helps preserve lean body mass and enhance lipolysis. Norepinephrine levels rise, contributing to increased alertness and potentially boosting basal metabolic rate. These hormonal shifts orchestrate many of the metabolic adaptations observed during fasting and play crucial roles in mobilizing energy stores and maintaining homeostasis in the absence of food intake.

3.8 Gut microbiome

The gut microbiome plays a critical role in overall health, influencing metabolism, immunity, and brain function. Fasting has been shown to significantly impact the composition of the gut microbiome. According to a systematic review [25], intermittent fasting results in an increase in beneficial bacteria, such as Firmicutes, and a decrease in harmful bacteria. These changes are associated with higher production of short-chain fatty acids, which offer various health benefits, including improved gut barrier function and reduced inflammation. Researchers also noted that these microbiome alterations coincide with increased browning of white adipose tissue, potentially enhancing metabolic health and aiding in weight management.

These effects suggest that fasting could contribute to improved health outcomes, such as better metabolic health, reduced inflammation, and enhanced cellular repair processes. However, it is essential to recognize that the effects of fasting can vary depending on the specific fasting regimen, duration, and individual characteristics.

4. Negative effects of fasting

Fasting, whether practiced for religious, weight-loss, or purported health reasons, can have significant adverse effects on the body if not approached cautiously. Again, the desired results may not be obtained if improperly done. For instance, a religious fasting like Ramadan offers valuable insights into brief food restrictions in healthy individuals. Contrary to popular belief, research suggests that Ramadan fasting does not necessarily lead to reduced food consumption. Studies have shown that energy intake either increases or remains steady before, during, and after Ramadan, despite fewer meals being consumed [26, 27]. Other potential negative effects of fasting include nutrient deficiencies, muscle loss, decreased metabolism, and electrolyte imbalances. It is therefore prudent to explore the potential negative effects of fasting as well.

One of the primary concerns is the risk of nutritional deficiencies due to prolonged periods without food, which can lead to inadequate intake of essential vitamins, minerals, and macronutrients [28]. This is particularly concerning for micronutrients that require regular intake, such as water-soluble vitamins. These deficiencies can weaken the immune system, impair cognitive function, and hinder physical performance [29]. In a study investigating adverse events and eating disorder symptoms during alternate day fasting [30], participants reported experiencing constipation in 17% of cases, water retention in 2%, dizziness in less than 20%, and general weakness in less than 15%.

For individuals with certain medical conditions or histories of disordered eating, fasting can exacerbate symptoms or trigger unhealthy behaviors [31]. Muscle loss is also a potential consequence, as the body may break down muscle tissue for energy when calorie intake is insufficient, especially if protein intake is inadequate [9].

Moreover, fasting can disrupt hormonal balance, particularly insulin levels, affecting blood sugar control and potentially increasing the risk of metabolic disorders [2]. Additionally, a study [32] suggests a potential disruption in menstrual cycles in women and affecting fertility due to fasting and dietary restrictions. Fasting also increases the likelihood of hypoglycemia in individuals with type 1 diabetes, posing a notable health concern [33].

Fasting has also been related to impaired cognitive function. Some people experience difficulty concentrating and decreased cognitive performance during fasting periods [34]. In their study on the impact of long-term fasting and intermittent fasting on cognitive abilities, researchers [35] discovered that both types of fasting could potentially impair cognitive function and decrease word production levels. In cases of prolonged fasting, reintroducing food too quickly can lead to refeeding syndrome, a potentially life-threatening condition [36]. Refeeding syndrome is a potentially life-threatening condition that can occur when severely undernourished individuals receive rapid nutritional support, either through tube feeding or intravenous methods. This syndrome is characterized by dangerous fluctuations in fluid balance and electrolyte levels, triggered by the body's hormonal and metabolic responses to sudden nutrient intake. These physiological changes can lead to severe medical complications [36].

It is important to note that the severity and likelihood of these negative effects can vary greatly depending on the individual, the duration and type of fasting, and their overall health status. Many of these risks are more pronounced with extended fasting periods or in individuals with pre-existing health conditions.

Therefore, while fasting may offer benefits when managed appropriately, it is crucial to consult with a healthcare professional, especially for pregnant or lactating mothers, individuals with eating disorder problems, as well as those with chronic health conditions, and approach fasting practices with awareness of potential risks.

5. Conclusion

During fasting, the body undergoes significant metabolic changes aimed at maintaining energy balance. Initially, the pancreas increases glucagon secretion as blood glucose levels drop, prompting the liver to release stored glycogen. Once glycogen reserves are depleted, the body shifts to burning fat and protein for energy. This metabolic switch involves processes like ketogenesis, where fat is converted into ketone bodies that serve as an alternative fuel source, especially for the brain.

Fasting also affects insulin sensitivity positively, potentially reducing the risk of type 2 diabetes. Cardiovascular health may improve, as evidenced by reductions in blood pressure and cholesterol levels. Autophagy, a cellular cleaning process, increases during fasting, promoting cellular health and potentially reducing inflammation.

However, fasting can have negative effects if it is not approached carefully. These include nutrient deficiencies, muscle loss, hormonal imbalances, and impaired cognitive function. Individuals with certain medical conditions or histories of disordered eating should be cautious, as fasting could exacerbate symptoms.

In summary, while fasting offers potential health benefits such as improved metabolism and cardiovascular health, it is essential to consider individual health needs and risks. Consulting with a healthcare professional before starting a fasting regimen is advisable, particularly for vulnerable populations.

Author details

Linda Afriyie Gyimah
Department of Food and Nutrition Education, University of Education, Winneba, Ghana

*Address all correspondence to: lagyimah@uew.edu.gh

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