Intermittent Fasting and Ketogenic Diet: A Comprehensive Review of Their Impacts on Human Health and Physiological System

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Abstract. This paper aims to explore the potential risks and effects of two means to lose weight that have become popular in recent years: intermittent fasting (IF) and ketogenic diet (KD). As these rapid weight loss methods have become popular on the Internet, they have triggered widespread attempts and discussions, especially among young people. Through a review of existing literature, this paper evaluates the effects of these two diets on five aspects: the immune system, metabolism, hormone balance, circadian rhythm, and intestinal flora. Studies have shown that IF and KD can promote lipid oxidation and reduce fat production in some cases, but they also inevitably bring side effects such as impaired metabolic health and interference with the biological clock. Although there is some evidence that these two diets have therapeutic potential for certain chronic diseases, there is still a lack of long-term, systematic follow-up studies to verify their long-term effects on hormone balance and intestinal flora. This paper comprehensively analyzes the potential hazards of IF and KD and puts forward suggestions for future research.

Keywords: Intermittent diet; ketogenic diet; weight loss; hormone balance.

1. Introduction

In recent years, the fad diet for rapid fat loss earns ever-growing popularity. On the fad diet, intermittent fasting (IF) and ketogenic diet (KD) are two most common forms (The number of average daily search volumes for both on google trends in 2023 is respectively 76-69, and 31-32).

From 2010 to 2022, the number of papers published on IF generally showed an increasing trend year by year, with a slight decrease in 2015 (159). From 2010 to 2018, the growth rate was slow (133 articles increased to 236 articles), and it began to rise rapidly in 2019 (47 more articles than in 2018), and the number of articles increased significantly in 2020 and 2021 (425 and 520 articles) [1].

IF especially refers to specifically to the periodic routines of not eating any food for a certain of time. In this review, it puts emphasis on discussing periodic fasting (PF), a unique model of arrhythmic fasting, which follows a combination of several continuous or non-continuous day of fasting within a specific timeframe [2]. People create a reduction of calories intake through skipping one meal or several meals rather than reducing the size of each serving [3]. The KD, which has a history of treating epilepsy, was developed In France as early as 1911 and was introduced in 1921. Dr. Wilder at Mayo Clinic officially proposed the KD. Today, the classical type is fundamentally represented by a quantitative diet combining fat with carbohydrates and protein, which is achieved by excluding high-carbohydrate foods while adopting high-fat foods [4]. In narrative review, it makes critical analyse and pertinent jeopardy and hazards discussion associated with two popular diets way to lose fat, including IF and KD. Particularly, it focuses on impacts of two fad diets' mechanisms on physical body involving the immune system, metabolism, hormone balance, circadian rhythm and gut microbiota. Numerous studies on IF's alternative treatment for patients with non-alcoholic fatty liver (NAFLD) [5] reveal improvement in lipid metabolism and liver enzymes. Also, the tightly controlled KD for children with intractable epilepsy is a reasonable non-pharmacological approach that contains potential therapeutic advantages aimed at curing epilepsy [6]. In addition, IF has also been shown to have pathological changes in gut microbiota -- notably altering the composition of gut microbiota, cecal and plasma metabolome, and preventing the progression of hypertension in spontaneously hypertensive stroke-prone rat [7]. A paper published in nature metabolism also shows

KD can induce a post-translational modification that is Lysine β-hydroxybutyrylation (Kbhb), which possesses therapeutic effects on multiple human diseases [8].

This review comprehensively analyzes potential risk behind alternative treatment and provides suggestions compared with scientific diet based on the experiments and literature of numerous biologists and nutritionists.

2. The Metabolic Mechanism of Food Digestion Process

2.1. Metabolic Mechanism of Overweight and Obesity

Since the IF and KD are both the way that start the trends of losing weight in short time period, before formally discuss their adverse effects, it is necessary to comprehend the definition of overweight and physiological changes in the normal body mechanisms during and after the digestion of food. Obesity is characterized by an accumulation of excess body fat to an extent that it negatively impacts health, differing from simple overweight conditions which also involve excessive fat deposits but do not necessarily impair health status. This chronic disease heightens the risk of various health issues, including heart disease, type 2 diabetes (T2D), compromised bone health, reproductive challenges, and a higher likelihood of developing specific types of cancer. Moreover, obesity can diminish an individual's quality of life by affecting sleep and general physical activity. Diagnosis of obesity is commonly facilitated through the measurement of body mass index (BMI), calculated as an individual's weight in kilograms divided by the square of their height in meters (BMI = weight [kg] / height^2 [m^2]). Patients are categorized based on their BMI into three groups: normal weight, overweight, and obese. According to BMI criteria, a BMI of 25 or higher denotes an individual as overweight, while a BMI of 30 or higher classifies them as obese. It's crucial to recognize that while BMI is a useful tool, it does not account for the distribution of fat or the ratio of fat to muscle mass.

2.2. Metabolic Pathway in Digestion

The body is constantly switching between eating and fasting situations constantly. Typically, food will stay in the stomach for about eight-three hours after chewing [9]. The hormones that control appetite and satiety and their mechanisms of action are complex physiological processes involving multiple hormones and their interactions in the body. Hormones regulate appetite and satiety by binding to specific receptors in the brain, activating or suppressing related neural pathways. For example, leptin, by binding to its receptors in the hypothalamic arcuate nucleus (ARC), inhibits the activity of neurons that promote appetite while activating neurons that promote satiety. Instead, ghrelin increases food intake and body weight by acting on neurons in ARC. The regulation of appetite and satiety is a complex network involving central and peripheral systems, including the hypothalamus region of the brain, the gastrointestinal tract, and the interaction of multiple hormones and neurotransmitters [10]. Normally speaking, after a meal, as the carbohydrates in food are digested and absorbed, the blood sugar levels begins to rise. It usually peaking about 1 hour after a meal, and then gradually decreasing to normal levels with the action of insulin. The whole process will finish in two hours after a meal in general. Additionally, the rise of blood sugar level stimulates the secretion of insulin, which helps cells absorb blood sugar and convert them into energy or store it as glycogen.

2.3. Changes Related to Metabolic Pathways

The gene related to fat is BMP2 gene which plays a significant role in the formation of fat cells. BMP2 gene can facilitate the differentiation of mesenchymal stem cells into adipocytes. During adipocyte formation, BMP2 gene affects adipocyte differentiation by influencing the expression of marker genes related to adipodifferentiation, such as ADD1, aP2, C/ EBP-α, GLUT-4, LPL, PPARγ, and SCD1. Moreover, the ability of BMP2 gene to induce fat formation is related to its concentration. Lower concentration of BMP2 can promote the formation of fat cells, while higher concentration may inhibit the formation of fat cells and promote the differentiation of bone cells. The

function of the BMP2 gene is also related to hormones, for example, BMP2, when combined with rosiglitazone or troglitazone, can promote the differentiation of pluripotent stem cells into adipocytes. This suggests that the presence of specific substances in the diet may influence fat cell formation through interaction with the BMP2 gene [11].

3. Disadvantages of IF

3.1. Effect on Human Hormone Level

There have been clear experiments to confirm the negative effects of IF on human reproductive hormones level. In obese premenopausal women, IF reduced male hormone markers, including testosterone levels and free androgen index (FAI), and increased levels of sex hormone-binding globulin (SHBG). Intermittent fasting (IF) tends to be more impactful when meals are confined to the earlier portion of the day. However, it appears to have minimal influence on hormone levels such as estrogen, gonadotropins, and prolactin in women. In men, particularly those who are lean and physically active, IF can lead to a decrease in testosterone levels without altering sex hormone-binding globulin (SHBG) concentrations. Notably, this hormonal shift does not seem to negatively impact muscle mass or strength. It's important to note that the research on how IF impacts hormone levels is still in its early stages, making it challenging to draw definitive conclusions. While IF might generally lower androgen levels in both genders, which could have various health implications if further substantiated by research, it's also possible that fasting could reduce androgens in men, potentially affecting metabolic health and libido. In summary, the effects of IF on hormone levels are subtle and not fully understood, with more research needed to clarify its impact on health outcomes [12].

3.2. Influences on Gut Microbiome

The gut microbiome is a community of microbes that live in our gut and interact closely with the physiology of their host. A review of the extensive literature, as well as evidence from numerous clinical trials, shows that, contrary to the originally assumed negative effects, IF has some positive improvements in gut microbiota. Studies have shown that IF improves metabolic health and may be beneficial in regulating sleep-wake cycles and eating habits. By altering the composition and function of the gut microbiome, IF may help boost metabolites produced in the gut, which are involved in regulating circadian rhythms. For example, short-chain fatty acids (SCFAs) produced by certain gut bacteria have been shown to affect the host's biological clock.

IF may indirectly affect circadian rhythms by reducing inflammation and oxidative stress, which are known to interfere with the normal functioning of the biological clock. During fasting, levels of adenosine monophosphate (AMP) rise in the body relative to adenosine triphosphate (ATP), a change that triggers the activation of AMP-activated protein kinase (AMPK). Activation of AMPK has important effects on a variety of biological processes: it increases levels of peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC-1 α), an important metabolic regulatory protein. AMPK also inhibits anabolic pathways, those metabolic processes that synthesize biomolecules and store energy, while promoting catabolic reactions such as autophagy, a cellular cleaning process that removes damaged proteins and organelles while improving mitochondrial function. In addition, studies have shown that time-restricted eating (TRF) can activate deacetylases, enzymes that can enhance the expression of circadian rhythm genes, which are essential for maintaining the normal functioning of the biological clock. Deacetylase activity is positively correlated with the abundance of gut microbiota, suggesting that TRF may influence host biorhythms by regulating gut microbiota, which may help prevent and treat obesity as well as disorders of glucose and lipid metabolism. At the same time, IF also promotes the oxidation of fatty acids by increasing the mRNA expression level of lipid droplet coated protein 5 (ADRP5), which helps to reduce cell damage due to oxidative stress.

More broadly, IF is able to trigger a range of cellular responses that are evolutionarily conserved and adaptable to improve and protect the organism's state. These responses include improved metabolism of blood sugar and lipids, increased resistance to stress, suppression of inflammation, enhancement of intrinsic defense mechanisms against antioxidant and metabolic stress, enhancement of DNA repair, and autophagy. These cellular responses work together to guide and improve the overall state of the body [13]. Research has revealed that intermittent fasting (IF) plays a significant role in modulating the daily rhythms of the gut microbiome, which includes an increase in the daily variations of both the number of bacteria and their activity levels. This modulation results in oscillations of signaling molecules generated by the gut microbiota, such as lipopolysaccharides, short-chain fatty acids (SCFAs), bile acids, and tryptophan metabolites. These molecules engage in communication with the host's biological clocks, both peripherally and centrally. By periodically binding to pattern recognition receptors on intestinal epithelial cells, these microbially-derived signaling molecules induce daily fluctuations in the expression patterns of circadian rhythm-related genes and their transcription factors. These genes and factors are crucial for the regulation of a variety of metabolic processes. Consequently, IF could assist in preserving the host's circadian rhythms and might offer valuable insights into managing and preventing rhythm-related disorders, including obesity and metabolic syndrome [14].

It is worth mentioning that IF has some specific or different negative effects on different groups of people. Existing experimental studies have shown that IF leads to more negative emotional states, such as irritability [15]. Some psychological effects are related to religion. Some of the religious subjects showed more positive emotions than others. The study also found that IF has different effects on different groups of people in some aspects, especially children and pregnant women. Headache, dizziness, polyuria, mood swings and drowsiness were the most common side effects. During periods of fasting, headaches are a frequent occurrence, typically attributed to hypoglycemia. These headaches are generally mild to moderate in severity and are often described as a diffuse, non-throbbing type. They tend to set in after an individual has fasted for a duration of at least 8 hours, with the intensity of the symptoms ranging from mild to severe [16].

4. Demerits of KD

KD’ effect on human body is sophisticated which can bring some benefits of metabolism but also has negative influence on it. The following is a summary and discussion of the negative effects of KD on the human body.

The KD may lead to increased stress on the endoplasmic reticulum (ER) and the Golgi, as well as changes in Golgi morphology, which may impair the transport of insulin particles. This ER/Golgi stress may be related to high fat intake in the KD, as lipid toxicity has been shown to cause ER stress and disrupt protein transport from the ER to the Golgi apparatus. Also, due to the dysfunction of the Golgi apparatus, it may lead to reduced insulin secretion, which affects the body's regulation of blood sugar, possibly leading to glucose intolerance. Long-term KDs may lead to dyslipidemia, including significant increases in plasma levels of triglycerides (TG) and non-esterified fatty acids (NEFA) [17].

The reduced consumption of carbohydrates during implementing KD for weight loss can cause decline in blood sugar levels which will result in hypoglycemic reactions like dizziness, blurred vision, diaphoresis, and fatigue. It is important to recognize that severe hypoglycemia can have profound negative effects on brain cells, potentially causing irreversible damage to the brain. In addition, excessive accumulation of ketone bodies in the human body may cause ketoemia [18].

What’s more, KD impairs islet function over long-term feeding through the result of time-course experiments. Sustained KD eating habits, will consume a lot of glucose in the body, difficult to adhere to. The whole body's regulation of lipid homeostasis will be challenged by the very high fat of the diet. In addition, it is worth noting that such eating habits contain a high probability of causing hyperlipidemia. Blood levels of triglycerides and free fatty acids increased significantly in both male and female mice on the KD. In addition, the male subjects also showed signs of fatty liver disease,

and their blood alanine aminotransferase (ALT) levels were elevated, which may point to degeneration of liver function.

4.1. Keto Flu

This is not a medically accepted term. However, in this context, it refers to the short-term side effects of the ketogenic diet, especially if there is a switch from a normal diet to a ketogenic diet and a reduction in carbohydrate intake. During the transition of diet, it is not a pleasure process that may cause people some common symptoms include: headache, fatigue, nausea, dizziness, "brain fog," gastrointestinal discomfort, decreased energy, feeling faint and heartbeat alterations [19].

4.2. KD's Effect on the Equilibrium of Hormone

Ketogenic diet (KD) has a significant effect on reproductive hormones in women with polycystic ovary syndrome (PCOS). Studies have shown that KD can improve hormone levels in PCOS patients, including lowering androgen levels, increasing sex hormone-binding globulin (SHBG) levels, and possibly improving LH/FSH ratios. These changes may have a positive effect on menstrual regularity and fertility. However, the long-term effects and safety of KD need more research [20].

4.3. KD's Influence on Circadian Rhythm

The core circadian clock, which is responsible for synchronizing all circadian oscillators found in the body's cells through neural and humoral signals, is based on a transcription-translation negative feedback loop. This central clock in the suprachiasmatic nucleus of the hypothalamus is aligned with light-dark cycles due to light input from the retina. It plays a crucial role in governing most physiological processes, including energy metabolism. The ketogenic diet induces a metabolic shift from carbohydrate oxidation to fatty acid oxidation by mimicking a fasting state. This metabolic shift may affect the expression of circadian rhythm genes and may lead to a rearrangement of metabolic gene expression. Food intake is an important factor in circadian rhythm. In particular, the macronutrient composition of foods, such as a high-fat diet, may affect the expression of clock genes and the function of the body clock. A ketogenic diet may affect circadian processes such as appetite, sleep, and hormone release by increasing the production of ketone bodies. Ketone bodies are not only a source of energy, but may also act as signaling molecules involved in regulating the body clock [21].

4.4. KD's Effect on Gut Microbiome

Research indicates that ketone bodies can selectively suppress the growth of bifidobacteria in the gut microbiome, which may lead to a reduction in pro-inflammatory Th17 cells within the gut. Moreover, ketone bodies participate in a range of metabolic processes that contribute to health benefits. These benefits potentially include enhancing mitochondrial function, boosting antioxidant and anti-inflammatory activities, acetylating histone and non-histone proteins, and regulating the acetylation of β-hydroxybutyrate on histones. Additionally, they modulate the neurotransmitter system and RNA function, which could slow down the aging process and the onset of associated diseases [22].

4.5. KD's Special Effect

In studies conducted on rats, the ketogenic diet (KD), which involves frequent deep fasting, has been shown to inhibit the biosynthesis of mitochondria and to trigger cardiac fibrosis. This dietary approach was observed to decrease mitochondrial production, curb cellular respiration, and ultimately result in the apoptosis of cardiomyocytes and the development of myocardial fibrosis. Furthermore, researchers discovered that beta-hydroxybutyric acid, a component of the ketosome and acting as an HDAC2 inhibitor, accumulates at higher levels during KD. This elevation in beta-OHB suppresses the transcription of genes that code for mitochondrial ribosomes, thereby hindering the process of mitochondrial biogenesis [23].

5. Conclusion

At present, the rapid weight loss method that is growing in popularity and catching fire on the Internet is eye-catching, and has caused many young people to blindly try. At present, there are many studies on the two diets discussed in this paper, IF and ketogenic diet in the long-term treatment of epilepsy, T2D meta-analysis. Objective To provide a review of potential risks. Based on the contents of several literatures, this paper provides high-quality evidence to support the effect of IF and ketogenic diet, two popular weight-loss diets in recent years, on five aspects of physical body's physical body, including immune system, metabolism, hormone balance, circadian rhythm, and intestinal bacteria. It is concluded that the two types of diet do have negative effects on the human body in different aspects, and the degree and effect of the impact vary from person to person. However, there is a lack of longer, more comprehensive follow-up experiments and studies on the lasting effects of both diets. The analysis and review in this paper concluded that IF and KD can indeed bring about similar increases in lipid oxidation and decreases in the production of new fat, but they inevitably bring about a series of effects that need to be carefully considered, including affecting metabolic health, interfering with the normal operation of the biological clock and a number of side effects. The corresponding literature review reference and relevant information summary are provided for future studies, but the more long-term effects of diet on various hormone balance and intestinal flora are still unresolved. In the future, hopefully, more studies or experiments will provide strong evidence of long-term effects. In general, the impact of the two diets on the human body is complex, but also need to consider personal health conditions, etc., carefully assess the potential risks.

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