The Effect of High-Fat Diet on Obesity and Potential Application of Ketogenic Diet

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Abstract. In recent years, the global overweight and obesity rate is increasing rapidly, which has become a serious problem threatening human health. With the rapid development of the economy, people have a very diverse choice of food, especially high-sugar, high-salt, high-fat diet. The high-fat diet contains a lot of Saturated and Unsaturated fatty acids, especially Saturated fatty acids. A long-term high-fat diet will make Triglycerides accumulate in the body, so it is more likely to induce obesity. At the same time, the ketogenic diet began to gain popularity around the world as an effective means of weight loss. By changing the way of metabolism in the body, the body is in a nutritional ketosis state, and the effect of greatly reducing body fat in a short time is achieved. In summary, this paper summarizes the causes of obesity by high-fat diet and the mechanism of ketogenic diet as an intervention for obesity and discusses the future of ketogenic diet in the treatment of Alzheimer's disease.

Keywords: High-fat diet; Obesity; Ketogenic diet.

1. Introduction

Obesity refers to a certain degree of obvious overweight and fat layer is too thick, is the body fat, especially the accumulation of Triglycerides caused by state. A person is only chronically obese if their energy intake exceeds their energy expenditure, and two key factors that affect energy balance are energy intake and physical activity [1]. The increasing prevalence of obesity today is mainly due to the increase in energy intake and the decrease in physical activity. Ultimately, obesity reflects an energy imbalance. Body Mass Index (BMI), a measure of underweight and overweight, defined as BMI≥25kg/m^2 for overweight adults and BMI≥30kg/m^2 for obesity, which is defined by the World Health Organization as abnormal or excessive fat accumulation that may harm health [2]. From 1985 to 2017, the global average BMI increased by more than 55%. Although the entire weight range became heavier, the change was greatest at the top [3]. In 2015, China and India had the highest number of obese children in the world, China and the United States had the highest number of obese adults, and Africa and Asia had the fastest growth of overweight and obesity prevalence [1]. Although the increase in obesity rates has slowed in developed countries over the past few years, the rate of increase has continued in developing countries. Obesity also increases the risk of other serious diseases, including cardiovascular disease, osteoporosis, certain cancers, sleep apnea, and behavioral and cognitive impairments. Obesity increases these risks independently and is also associated with other diseases.

At present, Obesity has become a serious global public health problem, and its high energy density, high fat diet is an important factor in causing obesity [4]. One gram of fat usually produces several times as much energy as one gram of protein or carbohydrate, with a high energy density. And the low satiety of fat sill makes people eat more frequently and in large quantities, resulting in excessive energy intake. At the same time, with the leptin resistance caused by long-term high-fat diet, it will also increase appetite and reduce the catabolism of fat. A variety of factors work together to make the prevalence of obesity continue to increase.

As an intervention, the ketogenic diet, a low-carb and high-fat diet, originally used to treat epilepsy, is now a commonly used by dieters. After starting a ketogenic diet for some time, the body's insulin production decreases and glucose is depleted. Gluconeogenesis takes place in the liver, converting non-sugar substances into glucose or sugar for energy. When these substances are consumed, ketone

bodies are generated under the stimulation of various hormones to provide energy for the brain and body. Ketogenic diet converts the energy provided by glucose into ketone body, prevents fat accumulation in the body, reduces hunger and significantly reduces food intake, which can effectively prevent and slow down obesity.

This article will introduce the health effects of high-fat diet, analyze the application of ketogenic diet in solving obesity-related problems, and the potential application of ketogenic diet in treating Alzheimer's disease.

2. The Effect of High-Fat Diet on Obesity

2.1. Definition And Composition By High-Fat Diet

High-fat diet refers to food with high fat content, which is specifically manifested as the composition of oil is a variety of saturated and unsaturated fatty acids. A long-term high-fat diet can lead to an imbalance of gut microbes and induce a variety of chronic diseases. Typically, a low-fat diet gets about 8-15% of its calories from fat, while a high-fat diet gets 40-50% of its calories or 60-80% of its calories from fat (causing obesity) [5].

There are many types of dietary fats, which can be divided into three categories according to saturation and unsaturation hydrocarbon chain (Fig. 1): Saturated fatty acids (SFAs), there are no unsaturated bonds in the hydrocarbon chain; Monounsaturated fatty acids (MUFAs), the hydrocarbon chain has an unsaturated bond; Polyunsaturated fatty acids (PUFAs) that have two or more unsaturated bonds in the hydrocarbon chain. A high-fat diet is rich in SFAs, which are more likely to cause obesity and liver fat changes than UFAs. And it increases the flow of dietary fat to the guy, leading to changes in the gut microbiome [6]. SFAs provide energy for human beings. Long-term high-fat diet leads to excessive intake of SFAs, which are acylated into TG and stored in fats, reducing the resting metabolic rate and diet-induced heat production of human beings, leading to obesity.

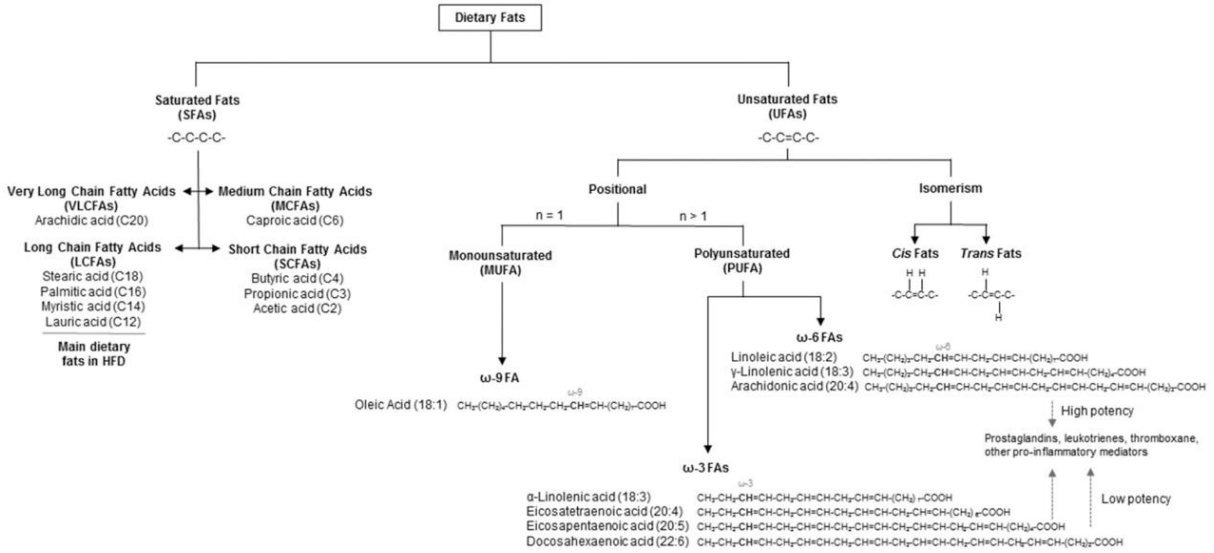

Fig. 1 The types of fatty acids [5].

2.2. Mechanisms of Obesity Induction by High-Fat Diet

2.2.1 Energy density

In normal human diets, manipulation of dietary fat content has consequential effects on energy density and on the proportion of other macronutrients, particularly carbohydrate [6]. The energy density of food is a decisive factor in energy intake. Some researchers have shown that high-fat diets induce obesity by increasing energy density. The energy density of food is closely related to the water and fat content of food. Fat content is the main factor in the energy density of various foods, and the remaining differences are mainly due to their water content. On average, 1g of fat produces 9kcal,

while 1g of protein and carbohydrates produce only 4kcal. So high-fat foods are energy-intensive. A high-fat diet for long time can cause excess energy and lead to obesity.

2.2.2 The satiating effect of fat

The human brain control sensations both and hunger and fullness. In the hypothalamus, there is a nerve center that controls appetite, which is divided into two parts: the satiety center and the feeding center. Glucose and free fatty acids are substances that stimulate these two centers. When after eating, the glucose in the blood increases, the satiety center is excited by stimulation, and people have a sense of fullness and do not want to eat anymore. When glucose in the blood is reduced, the body mobilizes lipolysis to supply energy, so that the free fatty acids in the blood increase, stimulate the feeding center, and produce hunger.

High-fat foods are energy-intensive and are a good source of stored energy. While there seems to be a minimal feedback impact on eating behavior when high-fat meals are consumed, there is evidence that fat in the intestines produces strong feedback signals. The term "The Fat Paradox" refers to the paradox that exists between the robust sensory cues that follow the consumption of fat and the inability of these signals to affect eating behavior [7]. Often the lack of satiety of high-fat foods and the human sensory preference will lead to more large and frequent eating, resulting in excess energy. If you drink two glasses of water before a meal (each cup is about 220ml), the stomach will have a temporary feeling of fullness.

Human ApoA-IV contains highly conserved, 22-amino-acid peptide repeats. The induction of ApoA-IV synthesis is mediated through absorption of long-chain fatty acids, but not short-chain fatty acids, which are transported via portal blood and do not elicit chylomicron production [8]. High-fat foods themselves contain pre-formed long-chain fatty acids. After entering the intestine, ApoA-IV generates new chylomicrons, the main components of which include triglycerides, cholesterol lipids and some carrier proteins. Therefore, high-fat diet will cause the expression of ApoA-IV to stimulate the increase of the secretion of triglycerides and cholesterol lipids in chylomicrons, thus causing obesity, accompanied by hypertension, diabetes and other diseases.

2.2.3 Leptin

The leptin gene was discovered in 1994 by Professor Friedman’s team at the Rockefeller University. Leptin, an important hormone that controls food intake and body weight, is and obesity gene product produced by adipose tissue [9]. It acts on receptors in the central nervous system, thereby regulating the behavior and metabolism of organisms. The content of leptin in serum is proportional to the size of animal adipose tissue. When an organism’s body fat increases, the serum leptin content increases, which in turn inhibits eating and accelerates metabolism. For leptin to cause anorexia, it needs to pass through the blood-brain barrier and get to the hypothalamus. Studies have shown that feeding a high-fat diet leads to a loss of neurons in the hypothalamus, in addition to a reduction in the integrity of the blood-brain barrier, which induces cardiovascular disease [10].

Leptin can promote lipolysis, and its effect is greatly diminished at maximum physiological concentrations. In the early stage of energy excess, with the increase of fat intake, leptin secretion increases, currently the level of serum leptin and fat content is positively correlated, acting on the hypothalamus, inhibiting appetite and promoting metabolism. And with a high-fat diet for a long time, it leads to excess energy. Further increases in leptin levels lead to decreased leptin sensitivity and leptin resistance, which decreases its ability to suppress appetite and boost metabolism, leading to increased obesity, and so on.

3. The Ketogenic Diet

3.1. Deification of the Ketogenic Diet

The ketogenic diet usually refers to a diet that is very low in carbohydrates (5-10%), moderate in protein (30-35%), and high in fat (55-60%) [11]. It mimics the state of hunger in the human body,

and the ketones produced by fat metabolism act as another source of body energy to produce anti-convulsive effects on the brain. The "classic" ketogenic diet usually refers to a medically supervised, extremely low-carb diet with a 4:1 or 3:1 ratio of dietary fat to dietary protein and carbohydrate. The ketogenic diet can boost spirits, boost metabolism and reduce overall body fat. The ketogenic diet was first proposed by Dr. Wilder in 1921 as a treatment for epilepsy. Ketogenic diet for simple obesity, under the high-intensity interval training method, improve the compliance of volunteers, reduce the weight and abdominal circumference, the effect is significantly higher than the conventional diet. In the 1970s, the ketogenic diet became popular as an effective means of weight loss.

Under normal circumstances, a small number of ketone bodies are produced in the human body, with the blood transported to the heart, kidneys and skeletal muscle and other tissues, as an energy source is used, the blood ketone body concentration is very low, generally not more than 1.0 mg/dl, urine cannot be measured ketone bodies. Due to the intake of the ketogenic diet, reduced insulin secretion leads to metabolic changes, and when the body is depleted of glucose or glycogen, fat becomes the main source of energy in the body. At this time, there is insufficient insulin in the body or a lack of sugar in the body, such as hunger, fasting, aggravated diabetes and serious pregnancy reactions, when lipolysis is excessive, the concentration of ketone bodies is increased, and some ketone bodies can be excreted through urine to form ketonuria.

3.2. Ketone Bodies and Energy Metabolism

Acetoacetic acid, β-hydroxybutyric acid and acetone are the intermediate products of the oxidative breakdown of fatty acids in the liver, which are known as ketones. Ketone bodies are fat, not glucose metabolites, so eating sugars does not lead to an increase in ketone bodies. However, when the glycogen store is saturated, the excess glucose entering the liver cells is converted into fatty acids. Due to the blood-brain barrier, other than glucose and fat cannot enter the brain to provide energy, ketone bodies can account for 25-75% of the brain's energy source during starvation, replacing glucose as the main source of energy in the body, but cannot be utilized by red blood cells and the liver. At the same time, ketone bodies are "super fuels", and the decomposition of ATP is far more than that produced by glucose, and at the same time, it can reduce the damage to free radicals and enhance the body's antioxidant capacity [12].

When hunger, fasting or a diet containing a small amount of carbohydrates for a period (the body's daily intake of carbohydrates is less than 50g/day), insulin secretion is reduced, and glucose is depleted [13]. Currently, with the participation of glucagon, gluconeogenesis is performed in the liver, converting a variety of non-sugar substances (lactic acid, glycerol, glycogenic amino acids, etc.) into glucose or sugar to increase energy in the body. Following that, the majority of the body's resources that are available for gluconeogenesis progressively run out. Hormone stimulation causes fatty acids to start breaking down in the liver's mitochondria, and the acetyl CoA that is created can have a variety of metabolic effects (Fig. 2). The most crucial step is, of course, to enter the citric acid cycle, continue the electron transport system, and ultimately complete oxidation to carbon dioxide and water; the other three are to act as precursors to fatty acid synthesis, produce cholesterol as a starting compound in cholesterol biosynthesis, and convert to acetone, D-β-hydroxybutyric acid, and acetoacetic acid, which are together referred to as ketone bodies. The first three ketone molecules (acetoacetic acid, beta-hydroxybutyric acid, and acetone) build up in the body throughout the ketogenic diet and act as a healthy substitute for ketosis. This other state is called "nutritional ketosis." Ketone bodies only generate very little acetone, which is quickly absorbed upon production. The blood carries acetoacetic acid and D-β-hydroxybutyric acid to the extrahepatic tissues, where they undergo oxidation. This process inhibits the production of further energy in those tissues, including bone, heart muscle, and kidney cortex, by means of the critic acid cycle. The brain generally only needs glucose as fuel, but it can also absorb acetoacetic acid or D-β-hydroxybutyric acid when glucose is scarce.

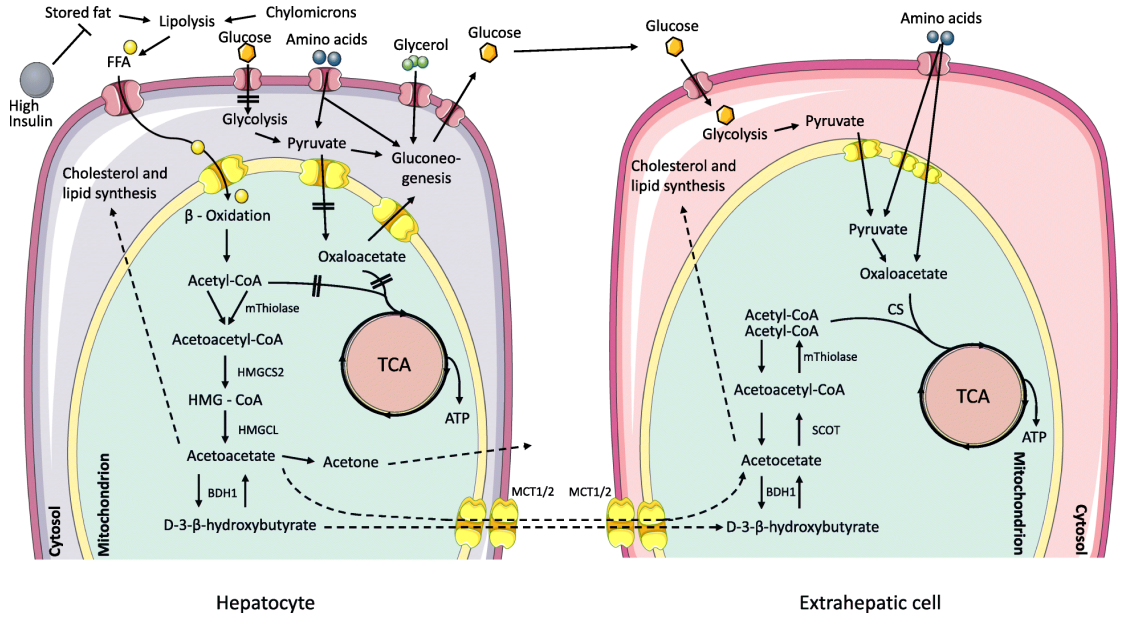

Fig. 2 Generation of ketone bodies and their metabolism [9].

3.3. Effects on Appetite Regulations

The ketogenic diet's unique macronutrient composition lowers appetite, which helps people lose weight by lowering hunger and compulsive food cravings. The ketogenic diet is associated with decreased or disappeared hunger, decreased desire to eat, and decreased overall appetite. After the body is satiated, insulin secretion increases, due to the reduction of lipolysis and inhabition of lipolysis, the fatty acids entering the liver decrease, resulting in the reduction of ketone body production. During starvation, the secretion of glucagon and other lipolysis hormones increased, the mobilization of fatty acid was strengthened, and the concentration of free fatty acid in blood increased, which was conducive to the β-oxidation of fatty acid and the formation of ketone bodies.

The ketogenic diet regulates appetite in several ways: maintaining a normal postprandial blood glucose response; After meals, raise blood levels of fatty acids to maintain hormone plumpness longer; Decreases food intake and perceived hunger instead of creating a sense of deprivation. The ketogenic diet is known to lower triglycerides. Leptin can control appetite by turning off Ghrelin's hunger signal signal, which affects appetite because high triglycerides inhibit leptin's ability to cross the blood-brain barrier. Leptin can singnal the brain and reestablish its dual role when Triglycerides are decreased with a ketogenic diet, which decreases appetite and spends up metabolism [14]. For whatever reason, comprartive studies have demonstrated that a low-car ketogenic diet (four percent carbohydrate) considerably lowers food intake and decreases appetite.

3.4.Risk of Ketogenic Diet

The blood ketone body concentration rises to an excessive level when the liver produces more ketone bodies than the extrahepatic tissues can use them, leading to ketosis, ketonemia, and ketonuria. Acetoacetic acid and β-hydroxybutyric acid in ketone bodies are acidic substances, and when accumulated in the blood, it can make the blood acid and cause acidosis, called ketoacidosis. During starvation, fasting, or on a ketogenic diet, the ketosis produced is “nutritional ketosis” (generally considered normal) and is substantially different from ketoacidosis, which is a harmful disease [15]. Ketosis is a disorder of globosity-lipid metabolism caused by poor use of glucose, and ketoacidosis is maintained as long as the body lacks carbohydrates, while ketoacidosis is related to the accumulation of ketone bodies, mostly due to the obvious lack of insulin leading to elevated blood sugar, resulting in hypertonic dehydration, electrolyte disorders, ketonuria, and metabolic acidosis.

Before starting a ketogenic diet, a detailed history and examination are needed to evaluate the type of attack; Rule out contraindications of ketogenic diet; Estimating risk factors for complications; Also

pay attention to whether the medication the patient is taking contains sugar. Because the ketogenic diet may have some common side effects, short-term side effects such as nausea, vomiting, hypoglycemia, acidosis, drowsiness, dehydration, food resistance, etc., these are mostly temporary and can be effectively dealt with. The long-term side effects include kidney stones, constipation, increased fat, growth disorders, abnormal bone metabolism and fractures, which require prompt medical treatment and stop the ketogenic diet. Since the ketogenic diet is a treatment in which fat replaces glucose as an energy source, those suffering from fatty acid transport and oxidation disorders are contraindicated.

4. Potential Applications in Alzheimer's Disease

The ketogenic diet can be effective in improving Alzheimer's disease [16]. Alzheimer's disease is a central neurodegenerative disease that occurs primarily in old or pre-old age, and the main features of the disease include progressive cognitive, with dementia being the most common form. The ketogenic diet is a widely used adjunct thereby for epilepsy, and recent research has shown that it may have therapeutic effects for psychiatric disorders, including Alzheimer's disease. Nuclear factor E2-related factor 2 (Nrf2), as an important regulator of endogenous oxidative stress, has been shown to reduce inflammatory responses. It can significantly delay early memory loss in mice, which is equivalent to mild cognitive impairment before the onset of Alzheimer's in humans or help prevent Alzheimer's disease [17].

The study demonstrated that ketogenic diet improved the cognitive function of Alzheimer's disease mice and reduced the deposition of amyloid plaques, glial cell proliferation and proinflammatory cytokines [17]. The anti-inflammatory effect of ketogenic diet is caused by the inhibition of NF-kB pathway activity by enhancing Nrf2/HO-1 signaling pathway. Therefore, these results suggest that ketogenic diet may have the potential to prevent the development of Alzheimer's disease because it can reduce the neurotoxicity caused by Aβ-induced inflammation. Amyloid is widely believed to be a key factor in the pathogenesis of Alzheimer's disease. Among them, Aβ1-42 subtype is more likely to aggregate and form Aβ plaque precipitate, which is the main pathogenic factor closely related to the progression of Alzheimer's disease. The immunofluorescence intensity of Aβ1-42 in hippocampus of APP/PS1 mice was much higher than that of WT mice. Compared with APP/PS1 mice treated with CD, APP/PS1 mice treated with ketogenic diet had a statistically significant reduction in Aβ plaque positive areas in the hippocampus ($P<0.0001$) and improved impaired working memory.

Although the ketogenic diet may have a certain effect on Alzheimer's disease, it should be mentioned that not everyone should follow a ketogenic diet, especially those with cholesterol problems, especially those with liver, pancreas and other diseases need to be carried out under the guidance of a doctor. At the same time, because the effects of the ketogenic diet on the human body still need to be further, it is recommended that it be carried out under the guidance of a professional doctor before adopting the ketogenic diet to treat Alzheimer's disease.

The ketogenic diet offers a glimmer of hope for the elderly as a new way to treat Alzheimer's disease. In the future, the ketogenic diet has great clinical guiding significance in the treatment of Alzheimer's disease and other neurodegenerative disease. With the progress of research, the mechanism of the protective effect of diet on human health will be better understood, and the treatment plan of other diseases will be more effective. The ketogenic diet will become a healthier and safer way to eat in the future, safeguarding human health.

5. Conclusion

The causes of obesity are complex and influenced by many factors, such as diet, region, culture, genes, age, lifestyle and so on. In this paper, we mainly study the influence of diet on obesity, especially the high-fat diet will lead to a large number of obese people, and mainly discuss some

mechanisms of obesity. The energy density of high-fat diet causes excess fat accumulation in the body, at the same time, due to the low satiety of fat, after eating, it still stimulates the nerve center in the hypothalamus that controls appetite, making more large and frequent eating. A long-term high-fat diet reduces the sensitivity of the leptin gene and causes leptin resistance. The interaction of various mechanisms causing obesity, coupled with people's sensory preferences for fat, and so the cycle, resulting in an increasing number of obese patients. As an effective intervention to prevent and slow down obesity, ketogenic diet explains the mechanism of its influence on obesity: The energy supply source in the body is replaced by ketone body, which breaks down fat to prevent the accumulation of Triglycerides in the body. Therefore, leptin can cross the blood-brain barrier to close the hunger signal and significantly reduce the intake of food, providing an effective way to prevent and slow down obesity. At the same time, it is proposed that ketogenic diet can help improve people's quality of life, and it has been proved that ketogenic diet can improve the cognitive function of AD mice, reduce the deposition of amyloid protein, and has a therapeutic effect on Alzheimer's disease. It also provides guidance on treatment options for other neurodegenerative disease. However, the existing evidence cannot fully support the effective effect of ketogenic diet on improving memory, and it is still in the animal experiment stage and has not been put into clinical trials, so there is a huge gap in the field of ketogenic diet in the treatment of neurodegenerative disease. However, the current study has relatively complete elucidated the mechanism of ketogenic diet on human health, whether it is to prevent obesity or treat other diseases, ketogenic diet will show greater efficacy in future studies.

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