

Analysis of Ketogenic Metabolic Interventions for Obesity

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ABSTRACT: According to statistics and surveys by the World Health Organization, the obesity ratio of people in the world nearly tripled since 1975; in 2016, more than 1.9 billion adults aged 18 and older were overweight. Obesity and overweight are defined as abnormal or excessive fat accumulation that presents a risk to health. Obesity prevention and intervention is a serious health problem facing humanity. This article is an analysis of interventions for obesity from the perspective of ketogenic metabolism, by supplementing exogenous ketones or increasing endogenous ketone levels. By analyzing experimental data on the metabolic mechanisms of ketones, exogenous ketones esters on body weight, food intake and satiety hormones, this paper concludes that exogenous ketones have a positive effect on interventions in obesity. A study of the literature revealed that the involvement of ketogenesis in the process of fat metabolism is still a very vague concept.

1. INTRODUCTION

Very early on, Hippocrates used starvation therapy to treat epilepsy, and Bible mentions starvation therapy as a method of epilepsy treatment. This therapy was used in the 19th century to treat refractory epilepsy in children. The ketogenic diet was once sought after by many people in the long fight against obesity, but the role of ketogenesis in the process cannot be determined, which is the reason why it has not been painfully effective in treating obesity, and as ketone metabolism is an important part of fat metabolism, people have reason to believe that it is inextricably linked to obesity.

This paper reviews the metabolic pathways of ketones and examines the characterization and control of important steps in them. This paper delved into previous experiments that have been performed and identified the key factors that influence the results. The positive effects of both exogenous and endogenous ketogenic interventions for obesity are compared, and to select a relatively safe and effective intervention and explore a more comprehensive treatment system. In the future, this has the potential to become a philosophy for the treatment of disease and post-rehabilitation.

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2. KETOGENIC METABOLIC MECHANISMS

2.1. Introduction to the Concept of Ketogenic Metabolic Mechanisms

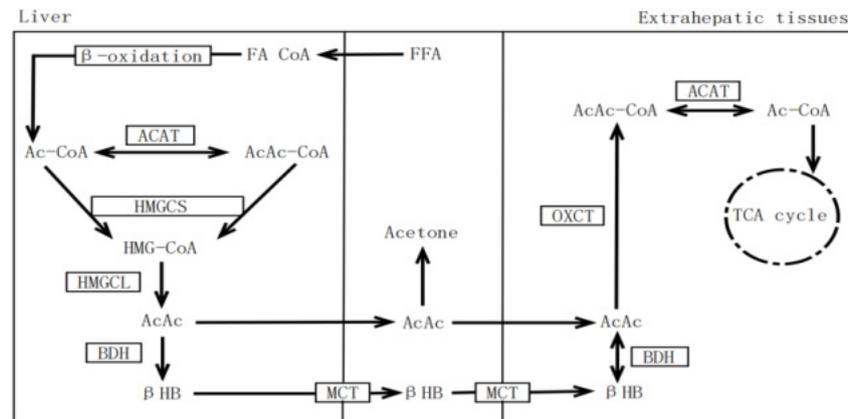


Fig. 1. ketogenic metabolic mechanisms

Figure 1 Ketogenic metabolic mechanisms

There are three types of ketones, including acetoacetate, acetone and β -hydroxybutyrate. In a normal human body, small amounts of ketone bodies are present in the blood in a ratio of approximately 78% β -hydroxybutyric acid, 20% acetoacetate and 2% acetone. Ketone bodies are intermediate products of free fatty acid metabolism. When liver glycogen stores are saturated, excess glucose entering the hepatocytes is converted to fatty acids, and when carbohydrate supply is reduced, for example during long-distance exercise, this is a time when ketone body metabolism is more likely to occur. Normally the liver produces trace amounts of acetone which is directly absorbed by the body. FFA (free fatty acids) in the liver produce acetoacetic acid (AcAc) in the presence of HMGCS (3-hydroxy-3-methylglutaryl-CoA synthase), ACAT (Ac-CoA acetyltransferase) and HMGCL (HMGCoA lyases), with most of ACAC reduced to β HB (β -hydroxybutyrate) in the presence of BDH (3-hydroxybutyrate dehydrogenase). When ketones are produced in the mitochondria of hepatocytes, AcAc-CoA is formed when the principal metabolites produced during β -oxidation of fatty acids mix in a process mediated by ACAT. HMGCoA (3-hydroxy-3-methylglutaryl-CoA) is produced when AcAc-CoA combines with another acetyl-

CoA via catalysis by HMGCS. HMGCL then cleaves HMGCoA, releasing AcAc and acetyl-CoA. AcAc can be converted to R- β HB (β -hydroxybutyrate reduced) or can be decarboxylated spontaneously to yield acetone. R- β HB is reoxidized to AcAc during ketolysis in extrahepatic tissues, before covalent activation of AcAc by CoA is catalyzed by OXCT (succinyl-CoA:3-oxoacid CoA transferase), resulting in AcAc-CoA. The thiolytic cleavage of AcAc-CoA by ACAT liberates two molecules of Ac-CoA, which are then integrated into the TCA (tricarboxylic acid) cycle. However, unlike ketolysis, R- β HB can also operate as a signaling molecule when it interacts with other molecules. The β HB originating in vivo and part of the β HB originating in vitro are transported by the blood to peripheral tissues where they are oxidized to AcAc in the presence of BDH. ACAC is the end product of ketogenesis, which in the presence of OXCT and ACAT produces acetyl-CoA (Ac-CoA). In the mitochondria, acetyl CoA (Ac-CoA) undergoes the TCA cycle to produce ATP (adenosine-triphosphate), and ketone bodies can also act as signaling molecules for a number of metabolic pathways, with increased levels increasing the efficiency of the mitochondria.

2.2. The Relationship Between Ketogenic Metabolic Mechanisms and Obesity

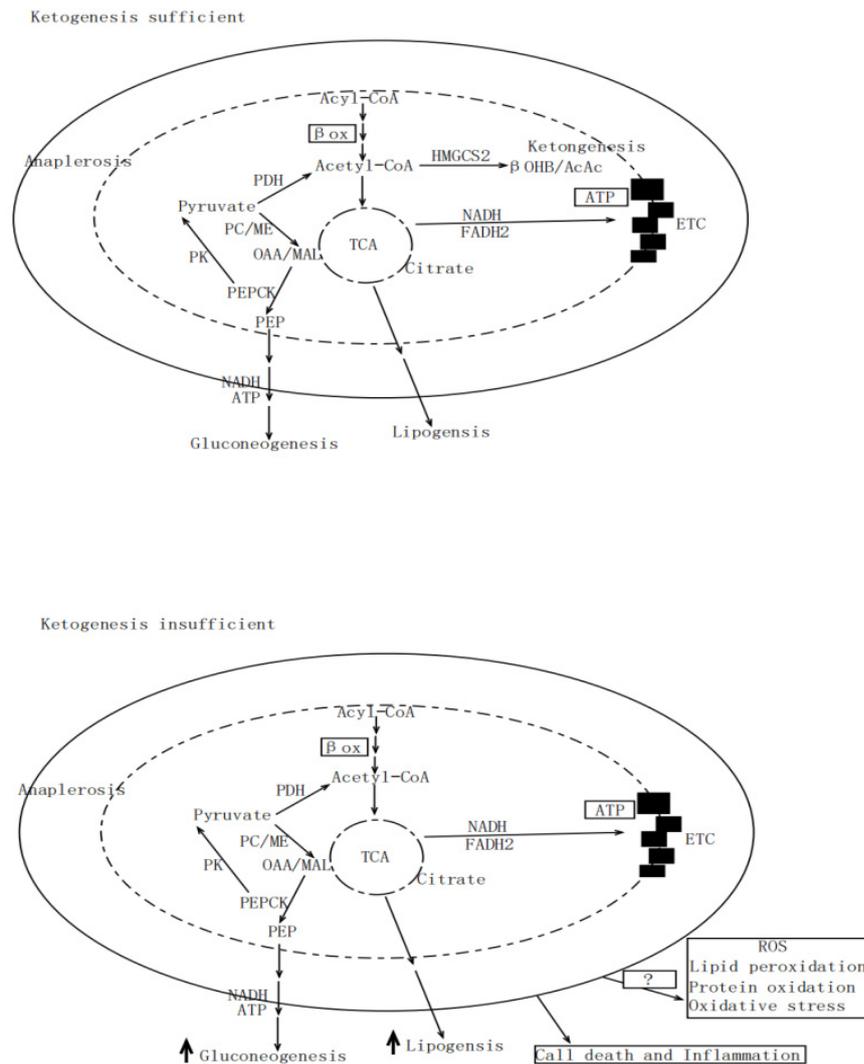


Fig.2. Ketone levels affect the metabolic process of fat

Figure 2 Ketone levels affect the metabolic process of fat

As shown in the figure above, mitochondrial acetyl-CoA can be directed to ketogenesis or terminal oxidation in the TCA cycle under homeostatic conditions, or exported to the cytoplasm for lipogenesis [8]. Lipogenesis and glucose production increase in the presence of ketogenic deficit. Increased acetyl-CoA disposal through the TCA cycle is stimulated by the loss of the ketogenic channel, potentially increasing the hazardous disposal of electrons into reactive oxygen species. Acetyl-CoA export to the cytoplasm for lipid-synthesizing pathways is also increased when ketosis is impaired. These changes are largely due to the changes seen in NAFLD (nonalcoholic fatty liver disease). The liver demonstrates increased lipid droplet esterification and lipolysis, increased β -oxidation of fatty acids, increased terminal oxidation, and enhanced gluconeogenesis in this situation, but decreased ketone body generation compared to fat availability. [8].

The amount of either exogenous or endogenous ketones in the body affects the amount of fat produced or metabolized. In addition, more experimental results have

shown that changes in endogenous ketone levels affect people's appetite, so it is reasonable to believe that there is an important link between endogenous ketone levels and obesity in humans.

3. ANALYSIS OF THE EFFECTS OF KETOGENIC METABOLIC INTERVENTIONS ON OBESITY

The ketogenic diet, a diet that consumes a high percentage of fat and a low percentage of carbohydrates, protein and other nutrients, has been used in the last century to treat refractory epilepsy in children. It is very effective for weight loss because it not only creates a calorie deficit, but also prioritises fat and ketone bodies to fuel the body and improve fat burning efficiency. Previous studies have typically described a ketogenic diet as a diet consisting of 50 grams or less of carbohydrates per day. Carbohydrates typically account for 5 percent to 10% of total calories [1]. Protein comprises up to 5% to 20% of the diet, while fat

makes up 75% to 90% [1]. The goal of the ketogenic diet is to induce ketosis, which is a metabolic state in which blood ketone concentrations are between 0.5 to 3.0 millimolar (mmol/L). There is not enough experimental data to prove the validity and reliability of the ketogenic diet. Therefore, experiments with a ketogenic diet over a period of time to demonstrate the relevance of ketone bodies in the process of fat metabolism and the feasibility of reducing body fat in the presence of ketosis are necessary.

The availability of fuel substrates, glucose and fatty acids, as well as glucagon, insulin, and cortisol hormonal

signaling, can all influence the rise in endogenous ketone levels. Exogenous ketones have been found to be a viable technique for rapidly boosting blood ketone levels and creating a state of ketosis as an alternative or to augment a well-formulated ketogenic diet. Furthermore, Matthew Stefan conducted research confirming the safety of exogenous β HB salt supplementation on safety and health indicators in adolescents [2,7]. Some of these experimental results showed that ketosis induced by beta hydroxybutyrate had no significant effect on changes in body fat (Figure 3).

	Pre	<i>d</i> (95% CI)	Day 90	<i>d</i> (95% CI)	<i>p</i> -Value
Total Mass (kg)					
BHB	52.67 ± 20.78	0.22(−21.09, 13.74)	53.47 ± 21.28	0.20(−20.91, 13.93)	0.8056
PLA	56.35 ± 11.96		56.96 ± 11.48		
Fat Mass (kg)					
BHB	15.40 ± 7.87	0.04(−6.69, 7.31)	15.12 ± 7.78	0.03(−6.79, 7.20)	0.6726
PLA	15.09 ± 5.96		14.92 ± 5.80		
Fat Free Mass (kg)					
BHB	37.27 ± 13.98	0.35(−16.04, 8.07)	38.32 ± 14.62	0.31(−15.78, 8.33)	0.6797
PLA	41.26 ± 8.51		42.04 ± 8.78		
Body Fat (%)					
BHB	28.29 ± 6.08	0.31(−4.59, 8.62)	27.38 ± 6.20	0.23(−5.07, 8.14)	0.1220
PLA	26.28 ± 7.03		25.85 ± 7.29		
Bone Mineral Density (g/cm²)					
BHB	0.91 ± 0.13	0.62(−0.21, 0.05)	0.92 ± 0.13	0.72(−0.22, 0.04)	0.0590
PLA	0.99 ± 0.13		1.01 ± 0.12		

Data reported in mean and standard deviation. *p*-value is from group by time interaction effect. 95% CI = 95% confidence interval of the mean difference between groups. *d* = Cohen's *d* between-group effect size [(BHB-PLA)/SD_{pooled}].

Figure 3 Body composition test results

The study was conducted on non-obese adolescents and the data and findings obtained may not be useful for people with obesity. The concentration of ketones was measured by venous blood measurements, but the metabolism involved in ketone bodies is a more complex process and does not mimic the ketosis environment by raising blood ketone concentrations alone. Possibly, these ketone bodies are not realistically taken up and utilised by the cells. It may be possible to determine the true amount of blood ketones taken up and utilized by the cells by isotope labeled method and isotopic tracer technique under the conditions of in vitro medium, which will further improve the accuracy of the experimental data results. In contrast, results measured by a ketogenic diet are more reliable, even if the targeting is not as strong.

Reducing hunger, regulating diet and psychological support are three effective approaches that have been involved in the treatment of obesity and have shown success, Ana I. Castro and Diego Gomez-Arbelaez demonstrated VLCK (very low-calorie ketogenic) diet following PNK (Medically controlled treatment that combines diet, exercise and coaching) method reduces food cravings while also leading to dramatic weight loss [3]. So far, the mechanism of action of birth ketones on appetite has not been studied, and there may be some related factors of action that may be present, which will be

the direction of continued research in the future.

Furthermore, compared to DEXT (isocaloric dextrose) drinks, exogenous ketosis following KE (ketone ester) beverages lowered two measures of appetite, hunger and desire to eat. This was accompanied by a drop in ghrelin levels, the hunger hormone. As a result, KE beverages provide a one-of-a-kind chance to isolate and utilize the effects of ketosis on hunger without requiring any additional dietary changes [4]. Even in calorie deficits, Angela M. Poff revealed that KDs (ketogenic diets) result in subjective perceptions of lower hunger and desire to eat (Figure 4), and these effects have been linked to the condition of NK (nutritional ketosis) [5]. Acute NK generated by the consumption of the R-BD (ketogenic precursors redenced) R- β HB monoester lowered subjective evaluations of hunger and desire to eat evaluated by visual analog scales, which correlated with ghrelin suppression [6]. Although the specific mechanism linking higher KBs to hunger hormone regulation is unknown and may include numerous organ systems, this is an example of a physiological function that both KDs and EKs (exogenous ketone supplements) appear to share. This not only points to a relationship between appetite and ketogenic metabolism, but also provides a unique direction for ketogenic metabolism to intervene in obesity, which will facilitate further research in the future.

	KDs	EKs
Total KB concentration	~0.5 to 5 mM (variable)	Ketone salts and KDE: ~0.3 to 1.0 mM KME: ~3.0 to 6.0 mM
R-βHB/AcAc	2:1 to 4:1	3:1 to 6:1
Time course of elevation in KB concentrations	Days to weeks	Minutes to hours
Adaptation period for metabolic effects	Suggested to be months to years; termed "ketoadaptation"	Unknown
Appetite	Suppressed	Suppressed
Glucose availability	Dietary intake of CHO < 5% of EI Circulating glucose concentrations lowered	Performance: coingested with CHO (~1 g·min ⁻¹ CHO) Health: acutely lower fasting glucose and attenuate postprandial glycemia
Lipolysis	Elevated Elevated FFA conc.	Attenuated Acute lowering of FFA conc.
Muscle protein synthesis	Unknown	Increased
Fat utilization during exercise	Markedly elevated IMTG utilization elevated	Measurement confounded IMTG utilization elevated
CHO utilization during exercise	Attenuated at high intensities	Attenuated at high intensities
Blood lactate concentrations	Unchanged or higher at same exercise intensity compared to mixed/high CHO diet	Attenuated rise during exercise

EI, energy intake; IMTG, intramuscular triglyceride; KDE, R,S-BD AcAc ketone diester; KME, R-BD R-βHB ketone monoester.

Figure 4 Compared to EKs, KDs achieve convergence and divergence characteristics between NK.

The DMTT (Dietary Medical Training Therapy) model should be advocated to treat obesity in a three-dimensional way. Using medical knowledge of human physiological and pathological structures and functions, we can accurately determine the cause of morbidity, accurately determine the cause of morbidity, and target treatment. Through the adjustment of daily diet to intervene in the intake of human nutrition, to assist in the treatment of diseases, to promote the recovery of the organism, as well as to effectively prevent the recurrence of the disease. Use scientific and systematic active training methods to control the training load and achieve improvement of body function. Use a variety of means of integrated treatment to achieve the most effective and rapid purpose. DMTT is the use of targeted - systematic - planned diet and training to treat maintain and improve non-normalized body functions and structures and help the organism to carry out normal physiological activities. It is part of a multidisciplinary rehabilitation philosophy and is an integrated and complementary approach to traditional treatment. It is hoped that this concept will provide a valuable research direction for the future of obesity treatment.

4. CONCLUSION

Treatment through a rational ketogenic diet is an effective form of endogenous ketogenic intervention, so the method of obesity intervention through ketogenic metabolic mechanism is worthy of recognition, which has a positive effect on the treatment of acquired obesity. Exogenous ketogenic interventions for the treatment of obesity have not yet yielded significant results, probably due to the limitations of current microscopic cytological studies and the fact that some of the factors that influence them have not yet been identified. Exogenous ketogenic interventions for the treatment of obesity still have not achieved significant results, probably due to the limitations of the current level of microscopic cytological research, and some factors that have not yet been discovered, as well as some substances that have not yet

been discovered to induce ketones. In the follow-up research, it is necessary to combine the medical, dietary and exercise perspectives, and the weight of the measures taken from each perspective is different, and the therapeutic effect may be different for different people, which also needs to be studied in detail, and this research needs to go through a long period of time and be based on a large amount of experimental data so that a relatively more comprehensive system for the treatment of obesity can be developed. This is the philosophy and approach advocated by the DATT model. It is hoped that in the subsequent research, more advanced treatment technologies such as gene therapy can be incorporated into this treatment system, which is believed to be more effective and faster in treating obesity, and can significantly reduce the treatment risks and side effects brought about by the treatment.

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