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The Preventive and Therapeutic Effect of Caloric Restriction Therapy on Type 2 Diabetes Mellitus

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1. Introduction

1.1. The definition of caloric restriction therapy

Caloric restriction (CR) is to treat some diseases by restricting the intake of calorie or the content of a particular ingredient of the diet, while ensuring the basic nutritional need [1]. It was used to increase average and maximum lifespan in ancient times [2], however, in last 100 years CR effect on improvement of T2DM has been established by many researchers, because it can improve the metabolic parameters and pancreas islet function of type 2 diabetic patients [3]. The treatment efficacy and safety has been clear.

1.2. The main forms of caloric restriction therapy

Nowadays, CR is only used in basic and clinical researches, and its form is disunity. The earliest form of this method used in the study is called fasting, which means apastia, and the participants should never eat anything except drink water. This method was eliminated because of its uncertain adverse reactions [4]. According to the different restricted objects of CR, it can be divided into low-calorie restriction diet, low-carbohydrate restriction diet, low-fat restriction diet and so on; according to the different frequency of CR, we can divide it into continuous CR, intermittent CR (followed CR for 2 days per week and normal diet at the other times) or every other day CR (followed CR one day and a normal diet the next day); and it can also be divided into short-term CR (≤ 9 days) and long-term CR (> 9 days) according to the length of restriction duration. Moreover, low-calorie restriction could be divided into low-caloric diet (LCD) and very-low-caloric diet (VLCD). All of them may improve the state of T2DM, control

the blood glucose stably and reduce its morbidity, but the differences of the treatment efficacy among them are not clear until now.

2. The preventive effect of CR on T2DM

As a lifestyle intervention method, it is very important to make sure whether this therapy can prevent T2DM from occurrence in the high risk persons. Tuomilehto et al. [5] had assigned 552 middle-aged, overweight subjects with impaired glucose tolerance to either the intervention group or the control group. Each subject in the intervention group received individualized counseling aimed at reducing weight, total intake of fat, and intake of saturated fat and increasing intake of fiber and physical activity. After 3.2 years follow-up, they found that the cumulative incidence of diabetes was 11 percent (95% confidence interval, 6% to 15%) in the intervention group and 23% (95% confidence interval, 17% to 29%) in the control group, moreover, during the trial, the risk of diabetes was reduced by 58% ($P < 0.001$) in the intervention group. The next year, another larger sample follow-up study focused on the lifestyle intervention on diabetes prevention, including CR, exercise, et al. Three years follow-up later, CR reduced the incidence by 58% (95% confidence interval, 48% to 66%), as compared with placebo [6]. These studies provided satisfactory evidences on the preventive effect of CR on T2DM.

3. The therapeutical effect of CR on T2DM

3.1. The short-term therapeutical effect of CR on T2DM

CR has shown to be helpful for the blood glucose control and the improvement of pancreatic islet function. It produces multiple beneficial effects on metabolic parameters in type 2 diabetic patients by virtue of both calorie restriction and weight loss. Animal experiments confirmed that CR regulates the process of glucose metabolism in a variety of tissues (adipose tissue, liver, pancreas, skeletal muscle, et al) [7]. In clinical trials, the blood glucose of the participators decreased to normal range within a few days, and to the lowest point after 1-2 weeks [8]. In another short-term study of 14 obese patients with T2DM using VLCDs, marked improvement was seen in glycosylated HbA1c [9]. It fell from $7.4 \pm 0.3\%$ to $6.0 \pm 0.2\%$ after 8 weeks VLCD [10]. As a consequence, CR was thought to improve glucose metabolism in type 2 diabetics. Besides, the fasting plasma insulin/C-peptide levels of patients with T2DM fell after CR, and thus improved the insulin sensibility [11]. Generally, Blood pressure, triglycerides, total cholesterol and LDL-C were reduced, while only HDL-C varied [12, 13].

3.2. The long-term therapeutical effect of CR on T2DM

Whether CR improves the state of T2DM for a long time has been the major concern for many researchers. Unick et al. [14] chose 5145 type 2 diabetic patients randomized to an intensive lifestyle intervention and diabetes support and education. The lifestyle interven-

tion group received a behavioral weight loss program that included group and individual meetings, a $\geq 10\%$ weight loss goal, calorie restriction, and increased physical activity. Diabetes support and education received a less intense educational intervention. After four years follow-up, body weight, blood glucose and lipid profile improved significantly in the intervention group, suggesting that CR may obtain an optimal long-term metabolic control in T2DM patients.

Because of the poor compliance of patients with long-term CR, there are few researches in this area, and more researchers begin to concentrate on the long-term effect of short-term CR on T2DM patients. In a clinical study, 40 obese patients with T2DM and symptomatic hyperglycaemia were selected despite combination oral anti-diabetic therapy +/- insulin, and given 8 weeks of VLCD therapy (750kcal/d), followed by standard diet and exercise advice at 2-3 month intervals up to 1 year [15]. After 8 weeks of VLCD, body weight and body mass index (BMI) fell significantly, with favourable reductions in blood pressure, fructosamine and HbA1c. Sustained improvements were evident after 1 year, with minimal weight regain. Unexpectedly, glycemic control tended to deteriorate. In another study, 18 insulin-treated T2DM patients were treated with 30 days VLCD (450kCal/day) with the cessation of all glucose-lowering medication, and then followed for 18 months [16]. Caloric intake was slowly increased to eucaloric and glucose-lowering medication can be restarted if necessary. After 18 months follow-up, the use of insulin was significantly reduced: 18 out of 18 patients on day 0, 5 out of 18 patients at 18 months. Moreover, although patients using insulin at 18 months had regained weight a little, but still had a better cardiovascular risk profile compared with this parameter before CR (Table 1). In spite of favourable outcomes, these shorter term CR studies still require more data to clarify the long-term therapeutical effect of CR on metabolic disorders.

3.3. The studies of special crowd for CR

Metabolic disorders including obesity and diabetes are more prevalent in children and adolescents. However, most of them cannot obtain a satisfactory blood glucose control since pharmacologic agents currently approved for use in children and adolescents with T2DM (metformin and insulin) are less optimal. Therefore, in hope of a better glucose control in children, lifestyle intervention attracted many interests. A chart review of 20 children (mean age 14.5 ± 0.4 years) who consumed a ketogenic VLCD in the treatment of T2DM was conducted [17]. Eventually, VLCD allowed insulin and oral agents to be discontinued in all but one subject who was not compliant, and no other subjects required resumption of medications during the course of the diet on the condition that the metabolic parameters such as blood glucose and blood pressure were well controlled. More importantly, this study monitored the metabolic profiles to ensure that the patients were not at risk for developing electrolyte disturbances or ketoacidosis. Fortunately, none experienced nausea, vomiting, dehydration, or other side effects, such as orthostatic dizziness, muscle cramps, fatigue or halitosis previously reported in pediatric studies.

The efficacy and safety of CR in the elderly were also investigated. Recently, a total of 5145 individuals with T2DM (1053 aged 65 to 76 and 4092 aged 45 to 64) were chosen to compare

the effects of 4 years of intensive lifestyle intervention in older and younger individuals [18]. Both groups were respectively divided into two subgroups and given either lifestyle intervention (include CR and exercise) or health education. After 4 years follow-up, lifestyle intervention was favourable to a better control of blood glucose, blood pressure. Surprisingly, the elderly group gained more benefits than the younger group. Therefore, CR may be considered to be a treatment to metabolic disorders.

4. The mechanism of CR of treating T2DM

In recent years, a number of studies have expounded the possible mechanisms from different sides of the CR studies.

4.1. Weight loss

It was thought that the effect of CR on blood glucose was similar to bariatric surgery, because both of them base on weight loss. Insulin sensitivity and blood glucose are improved after weight loss. However, it is still uncertain. An important issue is that blood glucose of patients fell before weight loss during 40 days VLCD [19]. Studies haven't been consistent with the effect of CR on obese patients with type 2 diabetes either. Bergman et al. [20] had compared the effect of CR on patients with normal BMI ($22.8 \pm 0.42 \text{ kg/m}^2$) and obesity ($36.1 \pm 1.548 \text{ kg/m}^2$), and found that both groups had a drop of hepatic glucose production volume after 12-48 hours CR, with a better improvement of the insulin sensitivity in normal BMI group. Recently, Unick et al. [14] divided the participants into overweight group, mildly obese group, moderately obese group and severely obese group according to their body weight, then they were treated with CR. The result showed that the overweight group lose less weight than other groups, but the change of other metabolic indicators was similar. This may show the change of body weight and metabolic indicators is not always parallel. So whether the effect of CR on the control of blood glucose was dependent on the weight loss is unclear now.

4.2. Glycometabolism

Firstly, CR inhibits gluconeogenesis, leading to the decrease of hepatic glucose output, thus reducing the glucose source; it increased fatty acid oxidation in the liver, and then produces ketones, which can improve the tolerance of hungry by inhibiting the appetite impulsion from hypothalamus; glucose metabolism and consumption in liver and muscles also increase after CR [21]. Secondly, CR increases the insulin sensitivity and reduces insulin resistance. When patients were recruited to evaluate the effect of VLCD, insulin resistance index significantly decreased eventually [22, 23]. However, it is still controversial. No contribution of CR on insulin sensitivity was found after 14 severely obese patients with T2DM were treated with VLCD for 7 days [10]. The short duration of VLCD and special population chosen may be responsible for this unsatisfactory result. Finally, CR improves pancreas islet function. The insulin secretion and the area under the insulin curve of OGTT increased after CR [24]. The

first phase insulin secretion, which represents acute insulin response, increased after CR as well. Therefore, CR was thought to improve pancreas islet function.

Figure 1 shows the effects of CR on glycometabolism. CR leads to glycogen depletion in muscle and liver, and restriction of carbohydrate leads to lipolysis and the formation of ketone bodies by the liver. Together, hepatic glucose output is reduced via inhibition of gluconeogenesis and glycogenolysis. Meanwhile, high protein stimulates insulin secretion and increases satiety. Circulating ketone bodies probably contribute to tolerability of the diet by suppressing appetite in the hypothalamus. Weight loss and diminution of fat depots in the liver, muscle and peri-visceral space lead to reductions in insulin resistance. Improved insulin sensitivity, dynamic insulin secretion and reduced hepatic glucose output lead to reductions in blood glucose levels.

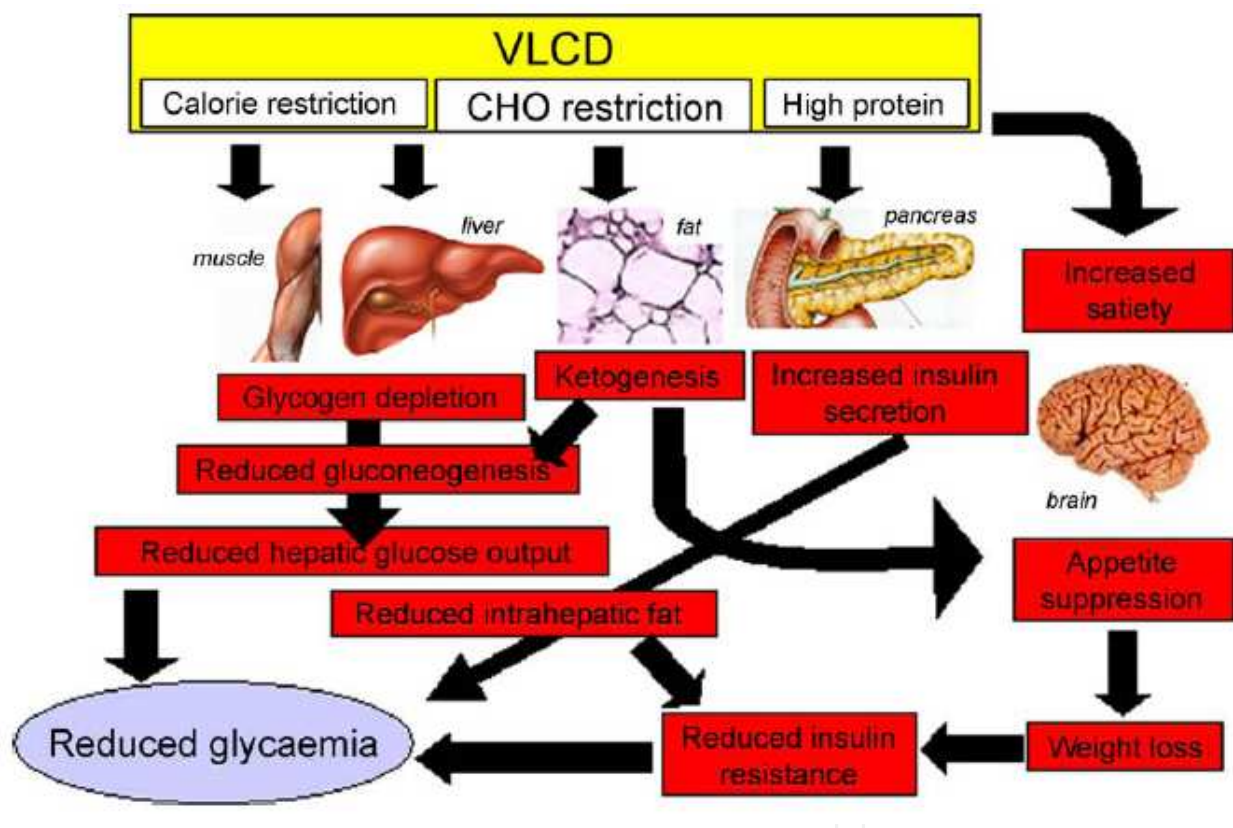


Figure 1. The effects of calorie restriction on glycometabolism. VLCD, very low calorie diet; CHO, carbohydrate.

4.3. Inflammatory response and oxidative stress

CR is “a new environment” to the human body. It causes lower blood glucose, insulin level, fat content and body weight. This helps human more tolerant to stress, thus some chronic diseases (T2DM, et al) could be prevented or treated [25]. Figure 2 has shown the effects of CR

on oxidative stress. CR results in an increase in the level and activation of adenine nucleotide translocase (ANT) and uncoupling protein (UCPs) to reduce the mitochondrial membrane potential, which induces a decrease in superoxide radical production at complex 1 of the electron transport chain. Less damage to the lipids in the mitochondrial membrane is further reduced by increases in the membrane lipid saturation. Increases in superoxide dismutase convert superoxide into hydrogen peroxide and increased levels of glutathione peroxidase (GPx) and catalase convert this to water reducing the product of the toxic hydroxyl radical (OH⁻) [26]. Lower levels of OH reduce the oxidative damage to proteins and DNA, which is further ameliorated by enhanced levels of degradation and base excision repair respectively. Animal experiments also confirmed that the oxygen free radicals in mice reduced and the β-hydroxybutyrate, which could act as an antioxidant, was increased after CR. In some clinical studies, some inflammatory factors (such as tumor necrosis factor-α, interleukin-6, interleukin-8) decreased significantly after CR.

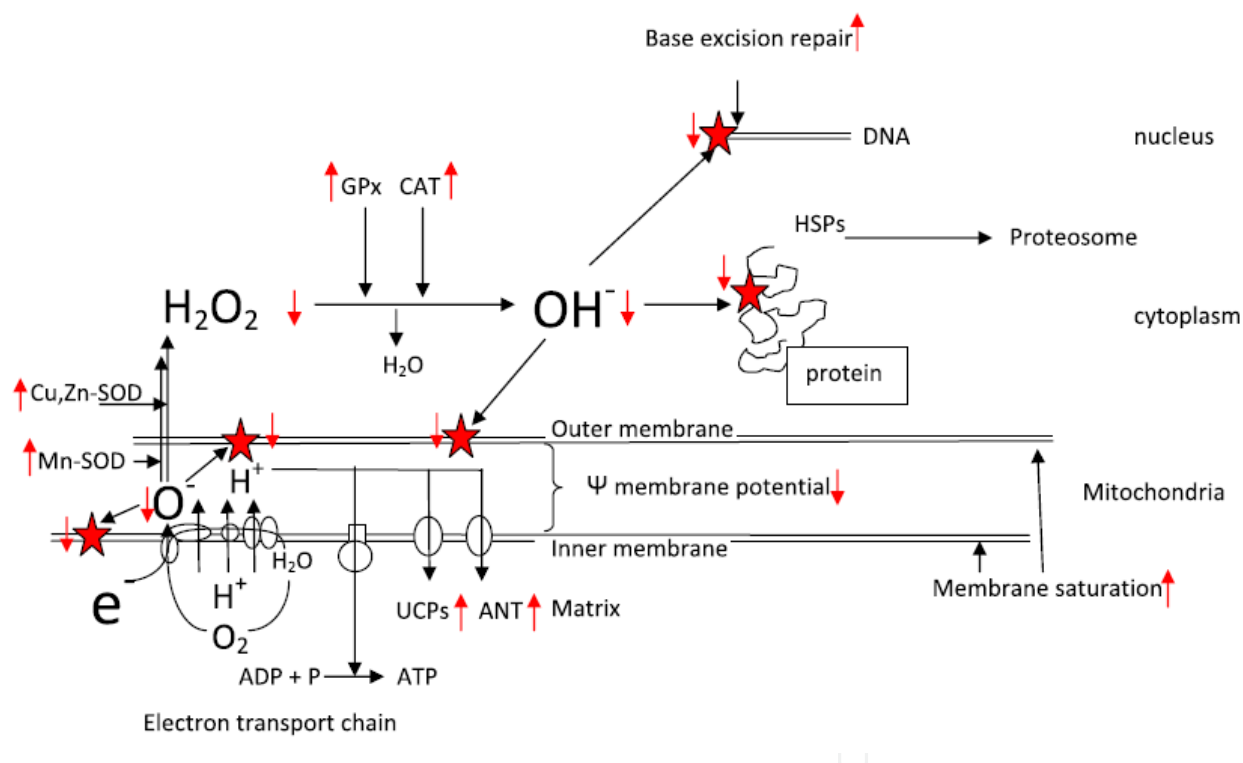


Figure 2. The effects of calorie restriction on oxidative stress.

4.4. Adiponectin

In 2011, Qiao et al. [27] found adiponectin gene expression increased in CR mice. Adiponectin in circulation could regulate various metabolic processes, including anti-inflammatory, insulin sensitivity and resistance, et al. It becomes another possible mechanism.

5. The differences among various forms of CR

Nowadays, the regime of CR in various studies is still not uniform. This causes imparity of CR effect. A systematic review published in 2004 showed that a very low calorie diet was associated with the most weight loss after 12 months in one small study with beneficial effects on asthma. There was no evidence that low carbohydrate diets were associated with greater long-term weight loss than low calorie diets. Nevertheless, they were associated with greater lowering of fasting plasma glucose and HbA1c than low calorie diets, with more adverse events, such as increasing risk of arrhythmia, osteoporosis or kidney stones [28]. Until now, there are few evidences from large-scale follow-up studies to clarify the differences among various CR forms.

6. The adverse reactions of CR

Strict caloric restriction may increase risk of hypoglycemia. There are not enough evidences that CR causes arrhythmia or electrolyte disorders in the studies reported until now [29]. The risk of gallstones may be higher in the first few days because of inadequate intake of fat. Bone density decreases during CR without any data showing it increases fracture risk. The most remarkable adverse reaction is increase of uric acid during CR, but only few study found it induced gout. CR may induce the onset of ketosis, which may depend on the total intake of carbohydrate rather than calorie [30]. However, the level of ketone bodies in serum during CR is generally 0.33-0.71mmol/l, which is far below the level during ketoacidosis (>25mmol/l), even though it is abnormal.

Other possible adverse effects include mild dizziness, headache, fatigue, cold, dry skin, transient rash, changes of defecate habits, hair loss, cramps, menstrual disorders and short-term elevated transaminases [31]. Yet for all that, these adverse effects are all slight, and can be treated easily. Generally, CR is relatively safe in patients with type 2 diabetes, but more long-term adverse effects needed to be observed.

7. The prospect forecast of CR used in T2DM

As a type of lifestyle interventions, CR may play a pivotal role in the therapeutic strategy to maintain optimal glycemic control and prevent complications in the patients with type 2 diabetes. In the light of the unreasonable lifestyle nowadays, CR should be paid enough attention to because it provides more choices for the prevention and treatment of T2DM. Existing studies cannot ensure uniform regime of CR for different state of T2DM. Large-scale and forceful researches are required to clarify the differences among all the forms of CR and the long-term adverse effects.

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