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Biology of Human Aging and Recent Nutrition Therapy

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Abstract

Discussion concerning Calorie Restriction (CR) and low carbohydrate diet (LCD) has continued for years. Authors have developed research of LCD using super LCD with 12% of carbohydrate. The biology of human aging includes study between human and mammalian such as mice, rhesus monkeys. Moderate CR reduced age-related mortality, incidence of diabetes, cancer, cardiovascular disease. By very low calorie diet (VLCD), body weight can be reduced, but the diabetic pathological state remains. Besides CR and LCD, Zone, Ornish, LEARN Diets and Mediterranean style can be applicable. There are very low-carbohydrate ketogenic diet (VLCKD), Moderate-LCD, High-Carbohydrate Diet, as related with the definition of LCD. Morbus (M) value was investigated for clinical practice of LCD, in which M value was remarkably improved by LCD treatment.

Introduction

Regarding nutritional therapy for metabolic and diabetic patients, the discussion has been continued for long concerning Calorie Restriction (CR) and low carbohydrate diet (LCD). Several investigators recently revealed the predominant efficacy of LCD compared with CR [1-3]. In western countries, Bernstein and Atkins originally launched LCD [4,5], which was effective and striking treatment at that time. After that, LCD has been more prevalent with the several efficacy in clinical practice [6-8].

On contrast, in Japan, authors and colleagues have started LCD and developed clinical research related with LCD [9,10]. We reported the significant role of ketone bodies in LCD and in physiological role of pregnant female and fetus-newborn axis [11]. We also continued medical and social development of LCD through Japan LCD promotion association, we proposed 3 types of actual LCD meal in daily life, which are petit, standard and super LCD [12].

Biology of Human and Animals in CR

The biology of human aging includes several investigation for anatomical, physiological and clinical similarities between human and other experimental materials and animals. They include yeast, worms, flies, mice, dogs, pigs, monkeys, and so on. Especially, some kinds of mammalian are recommended for its similarity with human.

Anti-aging medicine investigates and searches for speed against aging. From this viewpoint, discussion was found for years as to whether the lifespan is extended or the aging is delayed by CR. Among them, there are famous reports of rhesus monkeys over 20 years [13].

As a result, moderate CR reduced age-related mortality. In particular, CR reduced the incidence of diabetes, cancer, cardiovascular disease and cerebral atrophy. In comparison with control and CR group, the incidences of both neoplasia and cardiovascular disease was reduced by 50%. Especially, improvement in insulin sensitivity conferred by CR, has been consistent and remarkable [14,15]. Improved glucose homeostasis was maintained, inducing that diabetes was prevented by CR. Out of 38 control monkeys, 5 diabetes and 11 pre-diabetics were observed. In contrast, all animals on CR group revealed no glucose impairment. From these data, CR would possibly make aging slower in a primate species.

Humans are classified in the category of primates. Therefore, in medical research, it is expected that the results and information obtained by monkeys will be found in man as well. From the viewpoint of molecular biology, is that true in all cases? Lots of research have found concerning several experimental animals.

Transcriptional patterns of CR-animals suggest that CR retards the aging process by causing a metabolic shift toward increased protein turnover and decreased macromolecular damage [16]. The increase in longevity by dietary CR is coupled to profound beneficial effects on age-related pathology [17]. There is the reverse relationship between calorie intake and increase of lifespan in mice, suggesting a role for regulators of energy metabolism in the mechanism of CR. Consequently, metabolic reprogramming by induction of CR may be a crucial point in the mechanism for the extension of life span [13]. Investigations of yeast, worms, flies and mice would indicate a certain

role for nutrient which is responsive signaling molecules including SIRT1, mTOR and PGC-1α in aging and CR [18]. How are these findings related to the aging mechanism? The conservation of the effects of CR would depend on aging in primates.

Based on the above circumstances, attention was paid to whether the effects in monkeys could be seen in humans as well. A multicenter study involving 16 large facilities in the United States was conducted. Look AHEAD Research Group reported the results of multicenter study [19]. They included 5145 overweight or obese patients with type 2 diabetes mellitus (T2DM) and followed up 13.5 years. As a result, intensive lifestyle intervention focusing on weight loss did not reduce the rate of cardiovascular events.

Furthermore, the negative effect on musculoskeletal system [20] suggested in rhesus monkeys has also been confirmed in humans [21]. From the above, it is time to need a scientific re-evaluation on the effectiveness and safety of CR.

CR and VLCD

There was an impressive report showing the effectiveness and limit of Very Low Calorie Diet (VLCD) [22,23]. It shows the results of first 6 months from the Newcastle University to the British Diabetes Association Institute magazine [22] and several years' data [23] to the American Diabetes Association Diabetes Care. The protocol of the study is a long-term study in which 15 patients with type 2 diabetes carry VLCD for 2 months and CR for 6 months. Optifast® 624 kcal/day (PFC=34:19.5:43) was used for VLCD and then gradually increased the caloric intake. The judgment of remission of diabetes was less than 126 mg/dL of fasting blood glucose [22,23]. As a result of short-term vs long-term patients, body weight change and remission rate were of 99.0 → 84.5 kg, vs 96.9 → 83.0 kg, 86.7% vs 50.0%, respectively. In the latter, the fasting blood glucose did not decrease enough.

This study seems to suggest implications for diabetic diet therapy in the future. American Diabetes Association (ADA) previously mentioned the optimization of calorie as the most important task, because its aim was to acquire ideal weight [24]. In the countries where T2DM develops after obesity such as United States, eliminating obesity could be thought to decrease T2DM. Meanwhile, ADA stated in 2004 that CR diet cannot be maintained for a long time [25], and monitoring glucose intake has now become regarded as an important issue [26,27].

By this study, weight loss effect of VLCD became clear. However, even if the weight improves, the pathological diabetic state remains. Although visceral fat area drastically decreases and hepatic insulin resistance improves, elevated blood glucose persists. One of the cause is the continuation of intake for carbohydrates. Furthermore, it is not easy to actually live 8 weeks with a meal less than 700 Kcal a day. From the above, it would be rather difficult to aim for standard weight in application of CR.

Progress in LCD

After Atkins an Bernstein started LCD [4,5], several impressive research were reported. Atkins, Zone, Ornish and LEARN Diets were compared as well-known four dietary regimens [28]. Similary, Atkins, South Beach, Weight Watchers and Zone diets were also compared [29]. After that, Dietary Intervention Randomized Controlled Trial (DIRECT) group reported the efficacy of the LCD up to 2 years [6], and up to 6 year [7]. The effect of LCD plus Mediterranean-style diet was introduced with efficacy [30], which might be one of the better option in the future.

Formerly, the definition of LCD was rather vague. The effect of LCD over the years has been summarized, according to the percentage of carbohydrates [31,32]. Suggested definitions for different forms of LCD are shown in Table 1, which are very low-carbohydrate ketogenic diet (VLCKD), LCD, Moderate-LCD, High-Carbohydrate Diet [31-33].

Very low-carbohydrate ketogenic diet (VLCKD)
Carbohydrate, 20-50 g/day or <10% of the 2000 kcal/d diet, whether or not ketosis occurs. Derived from levels of carbohydrate required to induce ketosis in most people.
Recommended early phase ("induction") of popular diets such as Atkins Diet or Protein Power.
Low-carbohydrate diet: <130 g/day or <26% total energy
The ADA definition of 130 g/day as its recommended minimum.
Moderate-Carbohydrate Diet: 26%-45%
Upper limit, approximate carbohydrate intake before the obesity epidemic (43%).
High-Carbohydrate Diet: >45%
Recommended target on ADA websites.
The 2010 Dietary Guidelines for Americans recommends 45%-65% carbohydrate. The average American diet is estimated to be w49% carbohydrate.
Carbohydrate Consumption (NHANES).

Table 1: Suggested definitions for different Forms of low-carbohydrate diets [31-33]. (ADA: American Diabetes Association; NHANES: National Health and Nutrition Examination Survey; NHANES is a series of studies conducted since 1960 that monitors >5000 people. The content of this table is from some reports).

JAMA published the US dietary guidelines (the 2015 US dietary guidelines) [34]. In the guideline, an accurate revision of the Dietary Guidelines is crucial to the health of millions of people. Integral to this process is the Dietary Guidelines Advisory Committee (DGAC) report.

Research in LCD

In Japan, there are long history of CR and recent LCD treatment, because rice is our staple food for long years. Then, we can treat diabetic patients for CR or LCD and compare the treatment of in-patients and also out-patients.

Indeed, we have experienced many cases that blood glucose control improves with calorie restriction. However, its successful reason is that the disease duration is short and CR improves pancreatic first phase insulin secretion. Since active exercise therapy is also carried out in education hospitalization, insulin sensitivity of muscles will be improved even more [35]. On the other hand, patients with long duration would not have so effective results in CR treatment.

Furthermore, in the case of Japanese early diabetics, the mean BMI at onset is 24.4 and there are not many cases of obesity combined [36]. For even Japanese diabetics in early stages, will CR diets be really the first choice? Instead, LCD seems to be recommended because blood glucose would not be so increased.

The process for LCD development until now in Japan would be summarized as follows. The authors and collaborators launched the LCD [9,10] and NIPPON DATA 80 (National Integrated Project for Prospective observation of Non-communicable Disease and its Trends in the Aged 1980) reported 29 year data concerning the effect of LCD [37]. A research on RCT for mild restriction of glucose 130 g/day was reported [38]. Furthermore, we reported research of LCD with hypertriglyceridemia [39], with hyperketonemia in the axis of fetus-placenta-newborn-pregnant women [11], with renal function [40], with lifestyle habits [41], and so on.

In addition, super-LCD with 12% of carbohydrate has reduced blood glucose and M value in short period [39,40,42]. Morbus (M) value is the index which represents both blood sugar level and mean amplitude of glycemic excursions (MAGE) [43,44].

M value is calculated by the following formula: M=MBS+MW, where MW=(maximum blood glucose-minimum glucose)/20; MBS=The mean of MBSBS; MBSBS=Individual M-value for each blood glucose value calculated as (absolute value of (10×log(blood glucose value/120)))³.

$$M-value \frac{\sum}{N}\left|M\frac{BS}{BS}\right|+W/20 \qquad M\frac{BS}{BS}=\left|10\,log\frac{PG}{120}\right|^3$$
Where,

Regarding glucose variability, daily profiles of blood glucose has been measured 7 times a day, which data were calculated into average glucose and M value. Similar results were found on 7 times or 20 times of sampling per day [45,46]. It also revealed similar results compared with the continuous glucose monitoring (CGM) [47,48].

Daily profile of blood glucose and M value were investigated in 2 patients with T2DM [39,40,42] (Figure1).

The protocol was measuring glucose on day 0, 2, 12 from the start of LCD. There were remarkable decrease in glucose and M value by LCD [39,40,42].
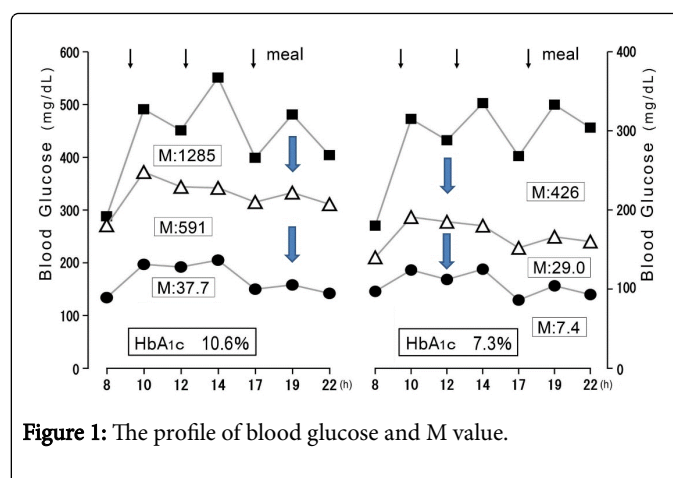

Figure 1: The profile of blood glucose and M value.

Conclusion

In summary, research on human and animal biology has continued for years. Among them, research on anti-aging medicine from gene expression to clinical practice has been remarkable for extension of life span. In fact, the importance of nutrition is becoming apparent, and it seems to be useful for improving people's health and lifespan.

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