



EDELWEISS PUBLICATIONS
OPEN ACCESS

Edelweiss Journal of Biomedical Research and Review

Commentary

ISSN 2690-2613

Ketogenic Diet is Beneficial from Hyperketonemia by Low Carbohydrate Diet (LCD)

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Citation: Bando H. Ketogenic diet is beneficial from hyperketonemia by Low Carbohydrate Diet (LCD) (2019) Edel J Biomed Res Rev 1:19-20.

Received: Oct 03, 2019

Accepted: Oct 18, 2019

Published: Oct 25, 2019

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Keywords: Ketogenic Diet, Ketone Bodies, Low Carbohydrate Diet, Non-Communicable Diseases, Beta-hydroxybutyrate.

Abbreviations: KD-Ketogenic Diet, KB-Ketone Bodies, LCD-Low Carbohydrate Diet, NCDs-Non-Communicable Diseases.

Introduction

Human being has been living on the earth for extremely long history. What was the living environment like in the ancient period? There was always a shortage of food associated with difficulty of survival [1]. Consequently, human was always fighting hunger and fasting for a long time. These severe conditions have influenced much for human evolution of metabolic flexibility [2]. As a matter of fact, hunger and fasting situation for human body has brought several benefits concerning human metabolic changes of hyperketonemia [3]. It may contribute human health with the metabolic research development nowadays. In this article, these topics would be described.

Concerning hyperketonemia, there has been various discussion of nutritional treatment of Low Carbohydrate Diet (LCD), weight reduction and Ketogenic Diet (KD). KD has been a special type of LCD, in which intake of carbohydrate is limited usually less than 50g per day. KD has been reported to promote metabolic health and protection against cancer and other Non-Communicable Diseases (NCDs) [1]. The mechanisms include decreased insulin levels, increasing mitochondrial substrate oxidation and specific anti-oxidative and anti-inflammatory effects of Ketone Bodies (KB) [4].

KD has been recently discussed in focus as one of the effective nutritional and diet therapy. The history of KD was initiated around 1920s for the treatment of epilepsy, autistic behavior and fasting in child obesity. The treatment of KD at that time was highly evaluated because of its satisfactory results [5]. After that, KD has been prevalent and applied to children with epilepsy across the world. In contrast, KD therapy for adult and elderly has been limited with rare experiences [6].

As metabolic syndrome such as obesity and diabetes has been recently so prevalent worldwide, KD has been in focus expecting the efficacy for these diseases. In order to reduce weight in such subjects, LCD was formerly introduced to health and medical field by Atkins and Bernstein. They had spread LCD with showing significant efficacy of reducing weight [7,8]. After LCD was a gradually accepted and well-known in European and North American country with successful results, author and colleagues have started LCD in Japan [9]. We have

continued clinical research of LCD for various patients and educational activities such as workshop and books for long [10]. For practical use of LCD, three LCD methods have been proposed and prevalent. They are petite LCD, standard LCD and super LCD, which has carbohydrate ratio of 40%, 26%, 12%, respectively [11]. Among them, super LCD has been equivalent to the KD. For example, total calorie intake per day is 1400 kcal/day. As carbohydrate ratio is 12%, then carbohydrate is calculated as 168 kcal/day, which equals to the amount of 42g of carbohydrate intake per day [12].

KD has been known to show several beneficial health and medical efficacy. The reason is due to elevated KB in the blood. Formerly, there was misunderstanding that hyperketonemia is believed to be risky clinical situation. In recent years, however, correct information has been known. They are i) elevated KB in blood is not risky matter except diabetic coma, ii) brain and muscle can use KB for energy production which is similar to glucose, iii) KB have anti-cancer effects proved by much evidence, iv) blood KB values show high in the axis of fetus, placenta, newborn and pregnant mother which suggests physiologically quite important roles for energy and growth by our research [13,14].

KB seems to have crucial metabolic function on growth in human. What is metabolic condition on animal species like? There are probably two metabolic pathways, which are i) the brains of neurologically precocial and mature species, ii) the brains of neurologically no-precocial and immature species such as rat and human [15]. The former case has the ability for complete oxidation of glucose, indicating aerobic glycolysis. In contrast, the latter has the ability of mixed metabolism for glucose and KB so as to generate synthetic and energetic activities [15].

In the case of mammals, there is the ability of converting energy stored in KB into high energy phosphates. KB can transport fuel particularly to the brain, heart and muscles in various conditions. They include fasting, starvation, nutrition treatment on LCD and circumstances of fetus and neonatal periods [16]. From comparison of animal species and related biochemical data, the fetus of most animals have been



raised and developed by the energy obtained from KB produced in the body [17].

Concerning KB which can yield much energy, there are clinically two types of active KB. They are beta-hydroxybutyrate (β HB, 3-hydroxybutyric acid, 3-OHBA) and Acetoacetic Acid (AcAc) [18,19]. These two can be converted to each other. The former occupies about 60-90 % in the blood and the latter 10-40% [20,21]. From the functional point of view, β HB has shown the main function of KB. Thus KB would always support the growth and survival of the mammals during energy deficits by becoming energy-producing engine as an alternative source of ATP.

There was an important data concerning the level of β HB. Healthy person usually shows 72-90 mg/dL of glucose and less than 0.2 mmol/L of β HB. Fasting elevates β HB, and its level is 0.3-0.5 mmol/L in 24 hours, 1-2 mmol/L in 2-3 days, 3 mmol/L in 3-4 days, and 4-5 mmol/L in 7-10 days. When obese patients continued fasting for 40 days, they did not show acidosis and their β HB values were 6-8 mmol/L [18,20].

Authors have reported the KB values on LCD in patients with Type 2 Diabetes Mellitus (T2DM) [21]. The intervention was super-LCD, which was the protocol meal with 1400kcal/day, 12% of carbohydrate and 42g of carbohydrate per day. KB levels were 0.16-4 mmol/L, and β HB levels were 0.14-3.58 mmol/L. The continuation period of LCD was from 4 to 28 days.

Recently, there is a new concept of "Neuroketotherapeutics" [22]. It shows a class of bioenergetics medicine therapies which feature the induction of ketosis. They include classic ketogenic diet, modified Atkins diet, fasting, ketone esters, medium-chain triglyceride supplements, and so on. The mechanism would be β -hydroxybutyrylation and lysine acetylation, and various effects would include reduced inflammation, attenuated oxidative stress, enhanced mitochondrial respiration, elevated neuronal long-term potentiation and altered protein post-translational modifications. Further investigation of neuroketotherapeutics will develop KB molecular biology and show new central nervous system therapeutic applications [22].

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