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Beneficial Effects of Ketone Bodies (KB) From Endocrine and Metabolic Points of View

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Abstract

The inaugural issue of "SunText Review of Endocrine Care" has been published. As the sun and moon shine during the day and at night, this journal will illuminate the world's medical community for long. When looking back the history of human being, the evolution of metabolic programs was observed. Under favourable and unfavourable environment, anabolic and maintenance program were continued, respectively. Food deficiency resulted in elevated ketone bodies (KB), which became important energy producing system in addition to glucose metabolism. Recent topics concerning KB include beneficial mechanism for cardiovascular disease, efficacy for neurodegenerative diseases and supplementation with exogenous KB.

Keywords: Ketone bodies (KB); β-hydroxybutyrate (β-HB); Low carbohydrate diet (LCD); Ketogenic diet (KD); Endocrine Care

Editorial Article

Congratulations for the inaugural issue of "SunText Review of Endocrine Care" [1]. As the sun and moon shine during the day and at night, this journal will illuminate the world's medical community for long. When looking back the long history, human beings have showed evolution for long years associated with metabolic change [2]. In favorable environment, growth and reproduction programs had been continued, which were anabolic metabolism. Under unfavorable environment, maintenance programs were engaged including dormancy and defence. Dormancy is induced by nutrient shortage relying on energy preserving catabolic metabolism. Defense is induced by infections and other aggressive factors with supporting anabolic metabolism [2].

Regarding human evolution, metabolic programs have changed during 4-7 million years [2]. There has been comparative perspective on two situations on fasting and binge eating [3]. Food deficiency resulted in elevated ketone bodies (KB), enhanced cognition, synaptic plasticity, neurogenesis, and neuro protection. This mechanism demonstrates optimal cognitive function and resistance to injury and illness. On the other hand, the latter has been recently observed in medical and health issues related to non-communicable diseases (NCDs) worldwide. Food abundance results in increased insulin resistance and cognitive complacency, leading to synaptic dysfunction, neurogenesis disorders, and neuro degeneration. This mechanism demonstrates suboptimal cognition and vulnerability to injury and disease [3].

From historical and medical points of view, recent topics would be described in this article concerning diabetes, KB, β-hydroxybutyrate (βHB), fatty acids, low carbohydrate diet (LCD), ketogenic diet (KD) and cardiovascular disease.

As an important study for diabetes, EMPA-REG OUTCOME has been known. Empagliflozin showed slower progression of CKD and lower rates of clinical events than control [4]. Regarding the protection efficacy for renal problem, KB seemed to be involved in the mechanism [5]. During the treatment of SGLT2i, rather persistent and mild hyperketonemia would be observed. In such circumstances, β-HB is taken up freely especially by the heart and is oxidized in predominance to free fatty acids (FFA). This automatic selection may improve the transduction of oxygen consumption for the efficient work at the mitochondrial level. Furthermore, the cardiorenal beneficial mechanism of empagliflozin would be from a shift in myocardial and renal fuel metabolism. This change seems to be from fat and glucose

oxidation with inefficient energy of heart and kidney, toward KB system with energy-efficient super fuel [6].

When insulin levels decrease or exercise is performed for a long time, free fatty acids (FFA) are mobilized from adipose tissue into the blood. From FFA, liver produces KB that exhibit beneficial effects on the heart with heart failure situation. Regarding the metabolism of KB, the fuel profiles of the heart and leg were investigated [7]. The human arterial-venous metabolomics were measured by the simultaneous blood sampling from radial artery, coronary sinus and femoral vein. As a result, the leg obtained about 90% of carbons from KB and glucose. In contrast, the leg released most carbons as lactate, FFA, and amino acids. In detail, approximately half of released FFA was C18:2 (linoleate), essential FFA, suggesting active lipolysis from adipose tissue. On the other hand, the heart showed that most carbons are from FFAs. KB were accounted for about 15% of carbon uptake in the heart, and acetate were about 2%, which is most abundant short-chain fatty acid [7]. As to clinically important point, the energy source would be switched from FFA to KB in the heart disease such as heart failure.

Thus, in heart failure, KB metabolism in the heart would be stimulated. It is not completely clarified whether this finding means protective to the heart, or conversely harmful to remodeling. According to the recent report, continuous intravenous infusion of KB improved cardiac output without increasing energy and oxygen demand [8]. In other words, KB can improve cardiac function without imposing a burden on cardiomyocytes. Furthermore, continuous intravenous infusion of KB has been reported to improve cardiac blood flow [9]. Thus, KB are considered to have a potential therapeutic effect on heart diseases centered on heart failure. Therefore, measures to increase the blood KB level may be effective.

As to cardiac function, hyperketonemia would bring several mechanisms with beneficial effects for protecting human organs [10]. There are 10 related factors in the following: i) elevation of cardiac energetics, endothelial function mitochondrial function, ii) reduction of cardiac remodelling, inflammation, oxidative stress, Histone deacetylase (HDAC, iii) related mechanism of blood pressure, body weight, blood glucose and lipid profile.

In addition to the above-mentioned cardiovascular system, KB have also been reported to be effective against neurodegenerative diseases. KD has been known to have historically efficacy for epilepsy and GLUT-1 deficiency [11,12]. It is also expected to be effective against mild cognitive impairment (MCI), Alzheimer's disease, and Parkinson's disease [13]. There was an impressive report that KB was effective against acromegaly, which is one of the endocrine diseases [14]. From the above, it can be considered that the protective effect of ketone bodies on brain cells can be observed.

Such an investigation would provide some answer for various inquiries. One question would be which is more effective, i) stabilization of glycemic fluctuations by LCD or ii) maintenance of hyperketonemia by some agent [15]. It has been reported that supplementation with ketone esters improved early insulin secretory response for 75gOGTT with alleviation of impaired glucose tolerance (IGT) [16]. For the background of this mechanism, hyperketonemia itself may contribute to the stabilization of glycemic fluctuations. From meta-analysis of RCTs, LCD showed better result than KD [17]. This reason would be probably easy continuation for the patients. Consequently, it would be a gospel method, if diabetic patient can have some medicine of KB precursors, associated with loose dietary restriction life.

In recent report, supplementation with exogenous βHB was provided [18]. Subjects included 22 healthy male and female adolescents, who consumed βHB 3.75g or maltodextrin placebo twice daily for 90 days. The analyzed factors were blood test, bone density, emotional intelligence and happiness surveys and blood pressure checked at 0, 45 day and 90 day. The result was well-tolerated and safe in the case of adolescence subjects [18].

In summary, several impressive information was commented. This report will hopefully become a reference for clinical practice and research development.

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