

## New Era of Metabolism from Glucose to Ketone Body with Beneficial Effects

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### ABSTRACT

In recent years, ketone bodies have attracted attention in the fields of medicine and health. In the light of anti-aging medicine, the ketone body metabolism system seems to be more medically advantageous than the conventional glucose metabolism system. Taking most advantage of ketone bodies, it is possible to prevent diseases and live a healthier and beneficial life.

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At first, ketone bodies contain three kinds on the medical practice side. They are 1) 3-hydroxybutyric acid (3-OHBA), 2) Acetoacetic acid (AcAc), 3) Acetone. 1) and 2) have action of ketone bodies, but 3) does not have activity like a burning residue. The molecular formula and the molecular weight of the ketone bodies are C<sub>4</sub>H<sub>8</sub>O<sub>3</sub> (MW 104), C<sub>4</sub>H<sub>6</sub>O<sub>3</sub> (MW 102), and C<sub>3</sub>H<sub>6</sub>O (MW 58), respectively.

Historically speaking, the ketone body was formerly called "an ugly duck of metabolism". The reason was that they were first discovered in large quantities in the urine of patients succumbing to diabetic ketoacidosis. Consequently, the doctors at the time tended to consider ketone bodies as toxic byproducts of impaired carbohydrate metabolism. After that, it has taken long years to accept that ketone bodies are normal metabolites.

When human has a prolonged fasting, ketone bodies can provide large amount of the brain's daily energy

requirement. After that, it has become one of the evidences that ketogenic response to fasting or starvation is a necessary metabolic adaptation designed to preserve strength and prolong life, in the lack of food for long.

Currently, correct knowledge that ketone bodies become energy sources has been widely spread. It is known that glucose with a molecular weight of 180 can pass through the blood brain barrier (BBB) in glucose metabolism. Likewise, it has been found that 3-OHBA and AcAc having molecular weights close to glucose can pass BBB through ketone body metabolism. When glucose availability would be diminished, ketone bodies produced in the liver from fatty acids mobilized from adipose tissue have the role of producing major sources of energy for heart, muscle and brain.

Ketone bodies have been in focus as arguments of diabetes, obesity, nutritional therapy for metabolic syndrome, Calorie restriction (CR) and Low Carbohydrate Diet (LCD). CR generally means fat limitation because it performs calorie calculation for food intake per day. In LCD, the amount of carbohydrate per day is reduced. In Europe and the United States, Atkins and Bernstein and others started LCD. In Japan, authors and colleagues have started LCD and many cases and related reports have been reported since. They include, glucose variability, Morbus (M) value, insulinogenic index (IGI)-carbohydrate-70g, urine C-peptide excretion, elevated ketone bodies in the fetus, placenta, umbilical cord, newborn and mother, ratio of 3-OHBA, AcAc and so on.

Regarding CR and LCD, the important point is the function of the insulin. For CR, in response to ingested

carbohydrates, insulin is secreted against elevated blood sugar. As insulin works to synthesize fat, fat tissue will increase in the body.

On contrast, for LCD, only small amount of carbohydrate is taken. Insulin continues basal secretion level with little additional secretion. Glucose metabolism does not work, while fat metabolism starts to move. Fat is burned and decomposed to produce ketone bodies. Here, the function of insulin would be a molecule that inhibits the synthesis of ketone bodies.

In comparison with CR and LCD, there is a recent report that CR could prevent the development of insulin resistance and impaired lipid metabolism by Li et al. Further study would be necessary concerning these situations.

As to both of CR and LCD, glucose system and ketone body have been involved. It can be considered with four axes.

1) The secretion amount of insulin is large in the former, and minimum in the latter. As the glucose system continues to operate, sooner or later, a decrease in insulin secretion or problems of insulin resistance can occur. In the latter case, since insulin is necessary for only basal level, it will not become diabetic unless there are serious problems in the liver and kidney.

2) For the problem of glycation, the former occurs, while the latter does not occur. In recent years, advanced glycation end product (AGE) which accumulates in the body related to glycation has been closely up. It is involved in the onset of chronic diseases including arteriosclerosis and dementia by AGE.

3) For oxidation of the substrate, the former has incomplete oxidation and the latter has complete oxidation. In order to obtain energy, the former needs to take more amounts of carbohydrates totally.

4) Warburg effect has been known as the predominant use of glucose anaerobically by cancer cells. Mitochondria of cancer cells are hardly working normally. It relies solely on incomplete oxidation of glucose with poor energy efficiency, and then a large amount of glucose is required. Therefore, cancer cells cannot utilize ketone bodies at all. Healthy cells can use both glucose and ketone bodies. From the above, it is impossible to grow cancer cells when glucose intake is minimized and the energy substrate in the body is converted from glucose to ketone body system. Recently, various effects of ketone bodies against cancer have been reported, and the use of ketogenic diet in cancer shows potentially promising, but inconsistent results.

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