

Editorial

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Wellness Fasting and Hyperketosis

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Ketoacidosis is sometimes a lethal complication of diabetes mellitus.¹⁻³ Ketone bodies are considered to be the toxic elements of ketoacidosis. Wilder³ considered that the threshold of ketogenesis (i.e. the maximal ratio compatible with the oxidation of the ketogenic compounds) was reached when the number of ketogenic molecules just equaled the number of glucose molecules. Each glucose molecule being ketolytic for 2 molecules of acetoacetic acid, the ratio is 2:1. As the glucose concentration exceeds 3 mM in the blood, 3-6 mM of ketone bodies in the blood would be considered to reach hyperketosis. Ketogenic food containing a high proportion of fat has been successfully used to treat epileptic fits resistant to medication.⁴ In a typical epilepsy diet, fat accounts for 90% of the energy intake. Such meals bring about changes in the enterobacterial flora.⁵

The production of adenosine triphosphate (ATP) is the key to energy homeostasis. In animal cells, glucose is successively transformed into pyruvic acid and acetyl coenzyme A or acetyl-CoA, the latter entering the tricarboxylic acid (TCA) cycle as a fuel. Alternatively, acetoacetate-derived acetyl-CoA is also used as fuel under circumstances of glucose depletion.⁶⁻⁸ At the time of a hypoglycemia, free fatty acids are produced from acylglycerol, becoming acetyl-CoA after beta-oxidation. At the same time, beta-oxidation produces excess amounts of acetyl-CoA, which successively turn into acetoacetyl-CoA and acetoacetic acid. This reaction mainly happens in the liver, and the produced ketone bodies are released into the blood. The peripheral cells of various organs absorb acetoacetic acid (and possibly β HB) to yield acetyl-CoA and use it as fuel.

We have reported the case of a lady who has been living happily on one cup of green vegetable juice per day for 18 years. We found that ketone bodies were used as energy source, reaching blood concentrations of 3136 μ M for 3 β HB and 635 μ M for acetoacetate.⁹ Considering that her meals contained only vegetable juice, enterobacteria should have contributed to the production of β HB. In the Koda's fasting therapy many intractable diseases showed remarkable improvements. In the light of recent scientific findings, this could be explained by a state of hyperketosis. "Fasting for wellness" is a new approach to improve longevity, recently elaborated by combining macrobiotics and slow physical training.

The relationship between intestinal microbiota and meals, and their effects on illness can be analyzed by sequencing 16s ribonucleic acid (RNA) or by deoxyribonucleic acid (DNA) meta-genome analysis.¹⁰⁻¹³ So far, bacteria of the *clostridium* genus are known to produce β HB^{14,15} and some strains could produce poly- β HB.¹⁶ Furthermore, many bacteria of the *furmicutetes* genus can produce butyric acid, which could be metabolized into β HB after absorption through enteric cells.¹⁷

Recently, β HB has been found to inhibit histone-deacetylase, a mechanism whereby gene expression is exquisitely regulated through chromatin remodelling.^{18,19} For example, the zinc-dependent mammalian histone-deacetylase (HDAC) family comprises 11 enzymes, which have specific and critical functions in embryonic development and tissue homeostasis. Furthermore, β HB acts as a ligand to the G-protein coupled receptor GPR109, which results in anti-inflammatory properties.^{20,21} These mechanisms could improve human health through antioxidant and anti-inflammatory pathways protecting against arteriosclerosis, myocardial damages, brain dysfunction, etc.²¹

A ketone supplement has appeared in European and American supermarkets since the end of 2014.²²⁻²⁴ It contains a diester of β HB and acetoacetic acid, β HB monoester, and β HB salt with Na^+ , K^+ or Ca^{2+} ions. This is a potential cause of gastrointestinal dysfunction and diarrhea. The excess intake of salt is also problematic.

In some clinical trials, the meal composition was 30% carbohydrates, 15% each of protein and lipid, and 30% ketone-ester. Athletes took 15.6 g of ketone supplement and exercised. Cox et al²⁴ reviewed five separate studies involving a total of 39 high-performance athletes. Ketosis increased the intramuscular oxidation of triacylglycerol during exercise, even in the presence of normal muscle glycogen and elevated insulin.

The authors suggested that this may hold clues to a better understanding of fuel metabolism in healthy persons, and represent a great therapeutic potential. In Japan, ketone supplements are not yet on sale. Instead, it is suggested to eat MEC (meat, egg, cheese) by 100 g/meal as a ketogenic meal.⁶ Coconut oil, avocado and olive oil are also recommended. Middle-chain fatty acids and caprylic acid are sometimes used, together with amino acids and lemon juice to remove the bad taste and smell.

I am not yet confident about the long-term health benefits of ketone supplements, because long-term follow-up studies are still lacking to clarify the risks in terms of mortality, cardiovascular diseases and cancer after high-protein, high-fat diets based on carbohydrate restriction.²⁵⁻²⁷ However, the mid-term intake of low-carbohydrate meals (around 30-40% carbohydrate) as developed by Ebe²⁸ and others shows benefits in diabetic patients.

However, many questions are still to be clarified, in particular the role of the enterobacterial flora. It could open a new field of research for the prevention and treatment of diabetes, inflammatory bowel diseases, autoimmunity diseases, neurologic diseases, and even for the stabilization of cancer in elderly people who cannot bear the surgery and side-effects of chemotherapy.²⁹⁻³¹

In this regards, wellness fasting should be reevaluated for its property to easily induce hyperketonemia.

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