METABOLIC EFFECTS OF THE VERY-LOW-CARBOHYDRATE DIETS: MISUNDERSTOOD “VILLAINS” OF HUMAN METABOLISM

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ABSTRACT

During very low carbohydrate intake, the regulated and controlled production of ketone bodies causes a harmless physiological state known as dietary ketosis. Ketone bodies flow from the liver to extra-hepatic tissues (e.g., brain) for use as a fuel; this spares glucose metabolism via a mechanism similar to the sparing of glucose by oxidation of fatty acids as an alternative fuel. In comparison with glucose, the ketone bodies are actually a very good respiratory fuel. Indeed, there is no clear requirement for dietary carbohydrates for human adults. Interestingly, the effects of ketone body metabolism suggest that mild ketosis may offer therapeutic potential in a variety of different common and rare disease states. Also, the recent landmark study showed that a very-low-carbohydrate diet resulted in a significant reduction in fat mass and a concomitant increase in lean body mass in normal-weight men. Contrary to popular belief, insulin is not needed for glucose uptake and utilization in man. Finally, both muscle fat and carbohydrate burn in an amino acid flame. Journal of the International Society of Sports Nutrition. 1(2):7-11, 2004.

Key Words: low-carbohydrate diets, ketogenic diets, ketogenesis, ketosis, diabetic ketoacidosis, ketone bodies, gluconeogenesis, insulin, glucagon, carbohydrate recommendations, glucose utilization, glucose transporters, fatty acids.

INTRODUCTION

According to the American Heart Association (AHA) Nutrition Committee, “Some popular high-protein/low-carbohydrate diets limit carbohydrates to 10 to 20 g/d, which is one fifth of the minimum 100 g/day that is necessary to prevent loss of lean muscle tissue.” Clearly, this is an incorrect statement since catabolism of lean body mass is reduced by ketone bodies (possibly through suppression of the activity of the branched-chain 2-oxo acid dehydrogenase), which and probably explains the preservation of lean tissue observed during very-low-carbohydrate diets. Unfortunately, the leading exercise physiology textbook also claims a “low-carbohydrate diet sets the stage for a significant loss of lean tissue as the body recruits amino acids from muscle to maintain blood glucose via gluconeogenesis.” Thus, it is certainly time to set the record straight.

THE KETONE BODIES ARE AN IMPORTANT FUEL

The hormonal changes associated with a low carbohydrate diet include a reduction in the circulating levels of insulin along with increased levels of glucagon. This activates phosphoenolpyruvate carboxykinase, fructose 1,6-biphosphatase, and glucose 6-phosphatase and also inhibits pyruvate kinase, 6-phosphofructo-1 kinase, and glucokinase. These changes indeed favor gluconeogenesis.
However, the body limits glucose utilization to reduce the need for gluconeogenesis. In the liver in the well-fed state, acetyl CoA formed during the β-oxidation of fatty acids is oxidized to CO$_2$ and H$_2$O in the citric acid cycle. However, when the rate of mobilization of fatty acids from adipose tissue is accelerated, as, for example, during very low carbohydrate intake, the liver converts acetyl CoA into ketone bodies: Acetoacetate and 3-hydroxybutyrate. The liver cannot utilize ketone bodies because it lacks the mitochondrial enzyme succinyl CoA:3-ketoacid CoA transferase required for activation of acetoacetate to acetoacetyl CoA$^3$. Therefore, ketone bodies flow from the liver to extra-hepatic tissues (e.g., brain) for use as a fuel; this spares glucose metabolism via a mechanism similar to the sparing of glucose by oxidation of fatty acids as an alternative fuel. Indeed, the use of ketone bodies replaces most of the glucose required by the brain. Not all amino acid carbon will yield glucose; on average, 1.6 g of amino acids is required to synthesize 1 g of glucose$^4$. Thus, to keep the brain supplied with glucose at rate of 110 to 120 g/day, the breakdown of 160 to 200 g of protein (close to 1 kg of muscle tissue) would be required. This is clearly undesirable, and the body limits glucose utilization to reduce the need for gluconeogenesis and so spare muscle tissue. In comparison with glucose, the ketone bodies are a very good respiratory fuel. Whereas 100 g of glucose generates 8.7 kg of ATP, 100 g of 3-hydroxybutyrate can yield 10.5 kg of ATP, and 100 g of acetoacetate 9.4 kg of ATP$^5$. The brain will use ketone bodies whenever provided with them (i.e., whenever blood ketone body levels rise). The blood-brain barrier transporter for ketone bodies is induced during starvation or very low carbohydrate intake, further promoting the flow of ketone bodies$^6$. This transporter has a $K_m$ that exceeds the concentrations of circulating ketone bodies that occur during starvation or very low carbohydrate intake, and a $V_{max}$ well in excess of energy demands$^6$. Therefore, ketone body delivery to brain will never be limited by this transporter. However, continued use of some glucose appears obligatory$^6$ and is supplied by way of hepatic gluconeogenesis. Finally, because of the inactivation of pyruvate dehydrogenase (by the low insulin concentration), the glucose that is used by tissues outside the brain is largely only partially broken down to pyruvate and lactate, which can then be recycled in the liver trough gluconeogenesis$^7$. Therefore, red blood cells, for instance, which have an obligatory requirement for glucose, are not depleting the body of glucose. Interestingly, Volek et al. recently reported that a very-low-carbohydrate diet resulted in a significant reduction in fat mass and a concomitant increase in lean body mass in normal-weight men$^8$. They hypothesized that elevated β-hydroxybutyrate concentrations may have played a minor role in preventing catabolism of lean tissue but other anabolic hormones were likely involved (e.g., growth hormone).

**DIABETIC KETOACIDOSIS VS. DIETARY KETOSIS**

Diabetic patients know that the detection in their urine of the ketone bodies is a danger signal that their diabetes is poorly controlled. Indeed, in severely uncontrolled diabetes, if the ketone bodies are produced in massive supranormal quantities, they are associated with ketoacidosis$^5$. In this life-threatening complication of diabetes mellitus, the acids 3-hydroxybutyric acid and acetoacetic acid are produced rapidly, causing high concentrations of protons, which overwhelm the body’s acid-base buffering system. However, during very low carbohydrate intake, the regulated and controlled production of ketone bodies causes a harmless physiological state known as dietary ketosis. In ketosis, the blood pH remains buffered within normal limits$^5$. Ketone bodies have effects on insulin and glucagon secretions that potentially contribute to the control of the rate of their own formation because of antilipolytic and lipolytic hormones, respectively$^9$. Ketones also have a direct inhibitory effect on lipolysis in adipose tissue$^{10}$. 
Interestingly, the effects of ketone body metabolism suggest that mild ketosis may offer therapeutic potential in a variety of different common and rare disease states. The large categories of disease for which ketones may have therapeutic effects are: 1) diseases of substrate insufficiency or insulin resistance; 2) diseases resulting from free radical damage; and 3) disease resulting from hypoxia.

THERE IS NO CLEAR REQUIREMENT FOR DIETARY CARBOHYDRATES FOR HUMAN ADULTS

Although some studies suggest that pre-exercise muscle glycogen stores determine capacity for prolonged exercise, there is no clear requirement for dietary carbohydrates for human adults. Current carbohydrate recommendations are based on 1) preventing ketosis, and 2) providing glucose beyond minimal needs. However, it is clear that ketosis is not harmful, except in the high levels seen in type 1 diabetes. Also, the need to provide glucose above minimal needs is exactly what has never been demonstrated. Indeed, the National Research Council has not established Recommended Dietary Allowance (RDA) for carbohydrates, probably because the human body can adapt to a carbohydrate-free diet and manufacture the glucose it needs. Nevertheless, some nutritionists contend that the carbohydrate is an essential nutrient. For example, Mcdonald claimed that healthy, moderately active adults require at least 200 g of carbohydrate daily to sustain normal brain metabolism and muscle function.

INSULIN IS NOT NEEDED FOR GLUCOSE UPTAKE AND UTILIZATION IN HUMANS

Contrary to popular belief supported by the leading physiology and biochemistry textbooks, there is sufficient population of glucose transporters in all cell membranes at all times to ensure enough glucose uptake to satisfy the cell’s respiration, even in the absence of insulin. Insulin can and does increase the number of these transporters in some cells but glucose uptake is never truly insulin dependent. Even under conditions of extreme ketoacidosis there is no significant membrane barrier to glucose uptake – the block occurs “lower down” in the metabolic pathway where the excess of ketones competitively blocks the metabolites of glucose entering the citric acid cycle. Thus, insulin is not needed for glucose uptake and utilization in man. In fact, the process appears to be general for all polar (water-soluble) substrates, as transporters are the mechanism by which they are transported across the highly non-polar (lipid) cell membranes. When insulin is administered to people with diabetes who are fasting, blood glucose concentrations falls. It is generally assumed that this is because insulin increases glucose uptake into tissues. However, this is not the case and is just another metabolic legend arising from in vitro rat data. It has been shown that insulin at concentrations that...
are within the normal physiological range lowers blood glucose through inhibiting hepatic glucose production \(^{21}\).

**FATS BURN IN A CARBOHYDRATE FLAME, RIGHT?**

It has been claimed that carbohydrates serve as a primer for fat catabolism (“fats burn in a carbohydrate flame”). However, as pointed out by Robergs and Roberts \(^{22}\), this is an incorrect contention. In skeletal muscle, fat certainly does not burn in a carbohydrate flame, as skeletal muscle does not have sufficient quantities of the enzymes to convert glycolytic intermediates into molecules that can be transported into the mitochondria to supplement citric acid cycle intermediates. Further, the production of acetoacyl CoA, a substrate of ketone body formation, can occur only in the liver and thus does not apply to skeletal muscle metabolism. Human skeletal muscle can oxidize at least seven amino acids: leucine, isoleucine, valine, glutamate, asparagine, aspartate and alanine. Of these amino acids, however, oxidation of only the branched chain amino acids (leucine, isoleucine and valine) appears to be increased during catabolic states such as exercise.

When muscle glycogen and blood glucose concentrations are low, the incorporation of the carbon skeletons from amino acids into the citric acid cycle is important for maintaining the concentrations of the intermediates, and therefore a high rate of mitochondrial respiration. Thus, both muscle fat and carbohydrate burn in an amino acid flame. As discussed by Robergs and Roberts \(^{22}\), amino acid catabolism during exercise is important for three reasons: 1) for free energy during exercise to fuel muscle contraction; 2) to increase concentrations of citric acid cycle intermediates and therefore support carbohydrate and lipid catabolism; and 3) to serve as gluconeogenic precursors.

It has also been claimed that carbohydrate provides the only macronutrient substrate whose stored energy generates ATP non-aerobically. This is not the case, however, since several studies have shown that amino acid catabolism also provides a source of anaerobic energy production \(^{23}\). Aspartate, for example, can be fermented to succinate or propionate \(^{24}\). Interestingly, Ivy et al. \(^{25}\) and Saunders et al. \(^{26}\), reported that the addition of protein to a carbohydrate supplement enhanced endurance performance above that which occurred with carbohydrate alone.

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