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Thematic Review Series: Calorie Restriction and Ketogenic Diets

## Ketone Strong: Emerging evidence for a therapeutic role of ketone bodies in neurological and neurodegenerative diseases

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Chronic inflammatory disease is emerging as a major health crisis in the US. Many Americans are suffering from a plethora of chronic inflammatory diseases including obesity, type 2 diabetes, cardiovascular disease, and cancer. Chronic and acute inflammation is also linked to several brain diseases that include epilepsy, Alzheimer's disease, Parkinson's disease, traumatic brain injury (TBI), and glioma. Diet and lifestyle issues contribute to the pathology of those suffering from these and other inflammatory diseases. Hence, the management of inflammation is one means of reducing the health burden from these diseases ([1](#), [2](#)).

Humans and other mammals have evolved to function for considerable periods without food ([2](#), [3](#)). While glucose is the primary fuel for the brain under normal fed states, the water-soluble ketone bodies,  $\beta$ -hydroxybutyrate ( $\beta$ -OHB) and acetoacetate, can compensate for glucose as a metabolic fuel for the brain and other organs under conditions of prolonged fasting ([4](#)). The liver makes ketone bodies naturally from fatty acids released largely from stored body fat (triglycerides). Changes in key hormones, insulin and glucagon, and regulatory genes orchestrate the physiological transition between the glucose-dependent fed state and the lipid-dependent fasted state. Although ketoacidosis was linked originally to the pathology of diabetes, physiological ketosis is generally linked to improved health. The difference in blood  $\beta$ -OHB levels distinguishes ketoacidosis (>20 mM) from physiological ketosis (1–8 mM). Acetone is a nonenzymatic degradation product of acetoacetate that can be easily detected in the breath of individuals with diabetic ketoacidosis (mostly type 1), or in those who conduct prolonged water-only therapeutic fasting.

Calorie restriction (CR) is a type of therapeutic fasting that has long been recognized as a means to improve general health, to manage a broad range of chronic diseases, and to delay aging ([2](#), [5](#)). Chronic inflammatory diseases produce oxidative stress that ultimately damages tissue biomolecules. Hyperglycemia can contribute to oxidative stress and inflammation ([1](#), [6](#)). Oxidative stress accelerates entropy, the thermodynamic basis for the aging process ([7](#)). CR reduces oxidative stress, which can delay entropy. The therapeutic effects of CR are associated with the reduction of blood glucose and the elevation of blood ketone bodies within normal physiological ranges. Veech ([8](#)) showed that metabolism of ketone bodies can reduce oxidative stress by increasing the redox span of the mitochondrial coenzyme Q couple, which reduces the amount of the Q semiquinone and thus oxygen radical production in cells with normally functioning mitochondria. It has been difficult to determine, however, if the major health benefits of CR are related to the elevation of ketone bodies, the reduction of glucose, or to the unique metabolic state arising from the combination of these effects. [Figure 1](#) illustrates the relationship of blood glucose and ketone body levels to the management of chronic inflammatory disease.

Although periodic water-only fasting can improve health ([9](#)), prolonged fasting will eventually lead to the

pathological state of starvation (10), while prolonged CR can lead to nutritional imbalances unless the nutritional composition of the restricted diet is carefully monitored. Nevertheless, emerging evidence indicates that dietary therapies, which lower glucose and elevate ketone bodies, are safe in children and adults, and are effective for a variety of neurological and neurodegenerative diseases (11). We recently showed that blood glucose is a major predictor of body weight in the C57/BL6 mouse strain (12). CR lowers blood glucose and body weight while elevating ketones regardless of the macronutrient composition of the consumed diet. Most popular weight loss diets are a form of CR.

A ketogenic diet (KD) is a low carbohydrate high-fat diet that was designed originally to manage seizures in children with epilepsy (13). The KD mimics the physiological state of fasting, which was known since the time of Hippocrates to reduce seizure susceptibility. An energy transition from carbohydrate metabolism to fat metabolism is thought to contribute to the therapeutic benefits of KDs. As with therapeutic fasting and CR, it remains unclear if the anti-epileptic and anti-convulsant effects of the KD are due to reduced glucose, to elevated ketone bodies, or to some combination of these effects. Circulating ketone levels become higher when KDs are administered in restricted amounts than when administered in unrestricted amounts (12, 14). We recently described how restricted KDs, administered with drugs and hyperbaric oxygen therapy, could help manage cancer (15). A similar therapeutic strategy could be used for managing neurological and neurodegenerative diseases.

The KD is a metabolic therapy that must be administered with care, as would be the case for any medical therapy. It should be recognized that unrestricted or excessive consumption of KDs, which elevate body weight, could potentially produce hyperlipidemia and insulin insensitivity thereby reducing therapeutic benefit (12, 14, 16). The high fat concentration of the KD will usually prevent excess consumption and body weight gain. As with CR, however, evidence indicates that KDs and ketone bodies can have powerful therapeutic benefit for a broad range of neurological and neurodegenerative diseases (11). Recent evidence indicates that the therapeutic effects of  $\beta$ -OHB against oxidative stress can arise through its action as an endogenous histone deacetylase inhibitor (17). These findings reveal how a global shift in energy metabolism from glucose to ketone bodies can regulate gene expression through epigenetic mechanisms. Synthetic ketone esters also appear to replicate several therapeutic features of KDs, but further studies will be necessary to establish these connections (18). The molecular mechanisms by which ketone bodies underlie therapy are now under active investigation. This Thematic Review Series will highlight current research related to the mechanisms of action and therapeutic potential of CR and KDs.

The first review of the series from Hashim and Vanitallie (19) provides a historical perspective of ketosis and ketones, the therapeutic potential of ketone bodies for disease management, and a segue to the other reviews. The review of Veech (20) highlights the bioenergetics of ketone metabolism and how this is linked to the role of ketone bodies as transcriptional regulators. Gano, Patel, and Rho (21) review the linkage between ketone body metabolism and mitochondrial function in relationship to the neuroprotective action of ketone bodies. Prins and Matsumoto (22) review the therapeutic potential of ketone bodies for TBI. TBI is now of major concern to the National Football League and to the veterans of the Iraq and Afghanistan wars. The KD could be an alternative or complimentary metabolic therapeutic strategy for managing malignant brain cancer (23). Woolf and Scheck (24) review the information supporting this possibility. The articles in this Thematic Review Series will stimulate further research into the molecular mechanisms by which global shifts in energy metabolism and ketone bodies act to reduce the pathology associated with inflammatory diseases of the nervous system. The *Journal of Lipid Research*, with its traditional focus on the science of lipids in health and disease, is an ideal forum for disseminating the information from this emerging field.

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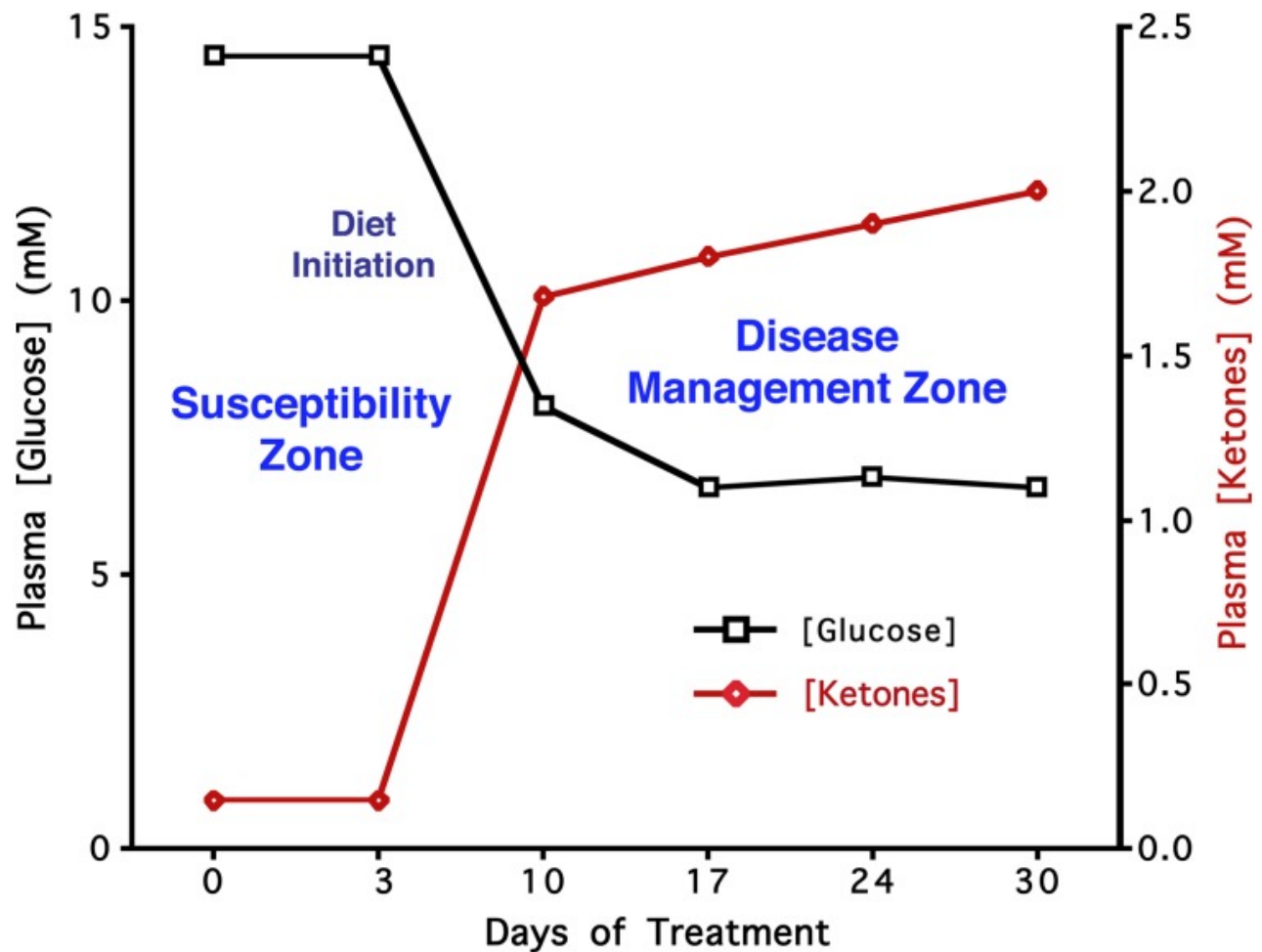
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## Figures and Tables

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**Fig. 1.**



Relationship of plasma glucose and ketone body levels to chronic disease management. The glucose and ketone ( $\beta$ -OHB) values are within normal physiological ranges under fasting conditions in mice and are linked to therapeutic benefit for epilepsy and brain cancer (25, 26). We refer to this state as the zone of disease management. The glucose and ketone levels predicted for disease management in humans are approximately 3.1–3.8 mM and 2.5–7.0 mM, respectively. It should be noted that blood glucose levels can be lowered and ketone levels elevated to a greater degree in humans than in mice under CR and fasting. This difference is due to the larger brain size and the lower basal metabolic rate in humans than in mice (9, 27, 28). Consequently, the therapeutic benefits of CR and KDs could be greater in humans than in mice. The figure is modified from (29).

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