Therapeutic Ketosis and Exogenous Ketones: Main applications and clinical updates

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Abstract

It has been recently shown that nutritional ketosis is effective against seizure disorders and various acute/chronic neurological disorders. Physiologically, glucose is the primary metabolic fuel for cells. However, many neurodegenerative disorders have been associated with impaired glucose transport/metabolism and with mitochondrial dysfunction, such as Alzheimer's/Parkinson's disease, general seizure disorders, and traumatic brain injury. Ketone bodies and tricarboxylic acid cycle intermediates represent alternative fuels for the brain andcan bypass the rate-limiting steps associated with impaired neuronal glucose metabolism. Therefore, therapeutic ketosis can be considered as a metabolic therapy by providing alternative energy substratesThe Ketogenic Diet (KD) represents a well-known therapeutic option for refractory epilepsy, although mechanisms regulating its anticonvulsant effects still remain partially unknown. Human brain derives over 60% of its energy from ketones when glucose availability is limited. After prolonged periods of fasting or during a Ketogenic Diet, the whole body utilizes energy obtained from free fatty acids (FFAs) released from adipose tissue. However, the brain is not capable to obtain significant energy from FFAs, thus hepatic ketogenesis converts them into ketone bodies: ß-hydroxybutyrate (BHB) and acetoacetate (AcAc), while a percentage of AcAc spontaneously decarboxylates to acetone. Recent perspectives about the Ketogenic diet potentials and neuroprotective properties strongly support its experimental and clinical application in a wide plethora of different neurological diseases. Notably, the metabolic state of mild ketosis, induced through Ketogenic diet administration, calorie restriction or fasting, may be used to metabolically manage epilepsy and number neurodegenerative syndromes, amyotrophic lateral sclerosis, and some types of cancer. In addition, the dietary intervention could represent a useful therapeutic support in some inflammatory nervous system-related neurodegenerative pathologies, such as Parkinson's Disease (PD). Therapeutic ketosis leads to metabolic adaptations that may improve brain metabolism, restore mitochondrial ATP production, decrease reactive oxygen species production, reduce inflammation, and increase neurotrophic factors' function. It has been shown that Ketogenic diet mimics the effects of fasting and the lack of glucose/ insulin signaling, promoting a metabolic shift towards fatty acidutilization.

In this work, the author reports a number of successful case reports treated through metabolic ketosis. According to the literature, the Ketogenic diet might exert its neuroprotective effect through an inflammatory cytokine and chemokine modulation with a resultant reduction of lymphocyte proliferation and an oxidative stress reduction. In fact, the cytokine/ chemokine modulation may prevent the activation of the inflammatory cascade with a consequent reduction in free radical production, also known as reactive oxygen species, ROS. In addition, this dietary regimen has shown an intrinsic antioxidant effect, considered the experimental observation in murine models for glutathione-peroxidase increased activity in the hippocampus while following a Ketogenic diet. In this light, the evident antioxidant properties of the Ketogenic diet may provide a significant neuroprotective effect against a number of neurodegenerative syndromes.

Furthermore, it has been observed that the Ketogenic diet can lead to an augmented expression and uncoupling protein activity (UCPs), which are proteins responsible for the mitochondrial transportation, which down-regulation seems to be associated to a higher susceptibility to the experimental autoimmune encephalomyelitis (EAE) activity, thus facilitating the inflammatory processes and the ROS production, leading to worse motor performances. Taken together, the experimental data suggest the adoption of Ketogenic diet for PD patients in order to restore the bio-energetic balance with potential neuroprotective effects, also due to a consistent improvement in L-Dopa absorption. In fact, it has been demonstrated in some animal models that one of the major metabolites, ß-hydroxybutyrate, can reduce the substantia nigra neuron loss and increase the oxygen consumption in mitochondria. The beneficial effects of Ketogenic diet on mitochondrial activity explains the improvement of patients' scores in Parkinson'disease.

Recently, an important concern that arose was that blood pH may transiently decrease during the initial phases of ketosis. This phenomenon is due to the accumulation of ketone bodies in the bloodstream, although a few studies have proved that the mild H+ load and blood pH physiologically return back to normal ranges as long as ketones are maintained below the value of 10 mM.

In addition, one of the hardest aspects to consider in this scenario is the common confusion about the physiological state of nutritional ketosis in the medical community: ketone bodies were previously consideredas "toxic metabolites", and thus usually caregivers associate the definition of "therapeutic ketosis" with "diabetic ketoacidosis", which is responsible for the well-known runaway ketosis and might lead to ketone bodies concentrations of 20 mM or greater. It is pivotal to underline that the difference between the two metabolic states; in fact, ketone blood concentrations during therapeutic ketosis can vary between 0.5 and 8 mM. Since the ketogenic diet (KD) is hard to get ready and follow, and viability of KB treatment in specific patients might be improved by raising plasma KB levels to ≥2 mM, KB esters,for example, 1,3-butanediol monoester of ßHB and glyceryl-tris-3-hydroxybutyrate, have been contrived. When managed orally incontrolled measurements, these esters can deliver plasma KB levelssimilar to those accomplished by the most thorough KETOGENICDIET, subsequently giving a sheltered, helpful, and flexible new wayto deal with the investigation and likely treatment of an assortment ofinfections, including epilepsy, AD, and Parkinson's sickness.