

# Clinical Applications of Ketogenic Diet-Induced Ketosis in Neurodegenerative and Metabolism- Related Pathologies

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## ABSTRACT

Metabolic-based therapies such as nutritional ketosis have been proven effective for seizure disorders and various acute and chronic neurological pathologies. In a healthy brain, glucose is the primary metabolic fuel for cells. However, neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), seizure disorders, and traumatic brain injury (TBI) are associated with impaired glucose transport and metabolism and with mitochondrial dysfunction leading to energy deficit. Therapeutic ketosis can be considered as a form of metabolic therapy by providing alternative energy substrates. In addition, ketosis leads to metabolic adaptations that improve brain metabolism, restore mitochondrial ATP production, decrease reactive oxygen species production, reduce inflammation, and increase the activity of neurotrophic factors. Moreover, the synaptic activity between neurons is also stabilized through the increase of Szent-Györgyi-Krebs cycle intermediates, antioxidant effects, increased GABA-to-glutamate ratio, and activation of ATP- sensitive potassium channels.

### Introduction

The Ketogenic Diet (KD) represents a well-known therapeutic option for refractory epilepsy [1], although mechanisms regulating its anticonvulsant effects are currently object of study [2]. The body is constantly producing small amounts of ketone bodies that, under physiological conditions, can make 22 ATP each, and it is regulated mainly by insulin. In a metabolic state of ketosis, ketone body production is augmented when circulating carbohydrates decrease or fatty acids blood levels are raised [3].

Although the mechanisms underlying the anti-seizure effects of the high-fat ketogenic diet (KD) remain unclear, it has been long-questioned whether ketone bodies (i.e.,  $\beta$ -hydroxybutyrate, acetoacetate and acetone) provide any contribution from a mechanistic perspective. In addition it has been investigated whether their effect is exploited in combination or alone [4]. It has been observed that ketone bodies are responsible for enhanced fatty acid oxidation and for a global shift toward intermediary metabolism. However, it has been shown that they are not pivotal for the diet's clinical effects [5]. This finding was proven by the fact that  $\beta$ -hydroxybutyrate blood concentrations

did not correspond to seizure control observations [6]. Nevertheless, it has been observed that  $\beta$ -hydroxybutyrate may interact with multiple novel molecular targets such as histone deacetylases [7], hydroxycarboxylic acid receptors on immune cells [8], and the NLRP3 inflammasome [9].

Overall, as a diet-based therapy is expected to render a broad array of biochemical, molecular, and cellular changes, no single mechanism can explain how the KD works.

Among diets developed to address health problems, the ketogenic diet has had a long and variable history. It was originally developed in the early 1920s at John Hopkins' All Children Hospital in Baltimore, MD as an alternative strategy to help children with epilepsy. Later, as pharmacological approaches became available and effectively addressed seizures, the diet fell out of favor [10]. During the last few decades, researchers and clinicians have learned and proven that it can be useful in children and adults with refractory epilepsy and a variety of other pathological conditions. This very high-fat diet almost fully takes carbohydrates off of the patient's food selection. The result is the substitution of ketone bodies as a source of energy. Today's ketogenic diet has been modified with scientifically proven adjustments to increase palatability and help with compliance. It has been proven to be effective for some forms of epilepsy (mostly refractory), and has shown to have neuroprotective effects in Alzheimer's disease, Parkinson's disease, and glaucoma. In addition, many patients are using it to lose weight and/or prevent obesity [10].

Human brain derives over 60% of its energy from ketones when glucose availability is limited. After prolonged periods of fasting or during a KD, the whole body utilizes energy obtained from free fatty acids (FFAs) released from adipose tissue. However, FFAs are insufficient to provide consistent energy for the brain, this is why hepatic ketogenesis converts them into ketone bodies:  $\beta$ -hydroxybutyrate (BHB) and acetoacetate (AcAc), while a percentage of AcAc spontaneously decarboxylates to acetone [11]. Recent perspectives

about the KD potentials and neuroprotective properties strongly support its experimental and clinical application in a wide plethora of different neurological diseases [12]. Notably, the metabolic state of mild ketosis, induced through KD administration, calorie restriction or fasting, may be used to metabolically manage epilepsy and a number neurodegenerative syndromes [13], amyotrophic lateral sclerosis [14], and some types of cancer [15,16].

In addition, epigenetics has been playing an important role in the world of ketosis. In fact, it has been shown how dietary restriction may delay the aging process associated with histone modifications. In this scenario, KD represents a valid therapeutic tool in inflammatory nervous system-related neurodegenerative pathologies, such as Parkinson's Disease [17,18].

According to the literature, the KD might exert its neuroprotective effect through an inflammatory cytokine and chemokine modulation with a resultant reduction of lymphocyte proliferation and an oxidative stress reduction [19]. 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 [20].

In addition, KD has shown an intrinsic antioxidant effect, considered the experimental observation in murine models for glutathione-peroxidase increased activity in the hippocampus while following a KD [21,22]. In this light, the evident antioxidant properties of the KD may provide a significant neuroprotective effect against a number of neurodegenerative syndromes [12,23].

Moreover, the KD has shown to have protective properties on the synaptic region of hippocampal sections undergone to metabolic deficit conditions induced by low glucose levels, correlated to up-regulation of genes coding for mitochondrial ATP-synthase [24].

Similar results have been observed in a relatively recent study, where ketone bodies have shown to provide protective effects on synapses after the mitochondrial respiratory chain inhibition, through an ATP production and antioxidant activity increase [25].

However, ketosis has also been observed to have detrimental effects on the nervous system. In fact, some relatively recent studies suggested that ketosis might accelerate the neurodegenerative process [26]. Furthermore, few works have been questioning about its side effects; notably, consultant pharmacists have addressed questions about the KD, its potential to correct or alleviate health conditions, and its limitations with an emphasis on the elderly [10].

In addition, it has been suggested that in many cases it is hard to obtain sufficient compliance from the patients. This is why it has been suggested that it might not be practical for most people to adhere to ketogenic diets continuously and alternative strategies are needed to harness the brain- protective potential of ketone bodies [27].

Furthermore, it has been observed that the KD 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 [28], thus facilitating the inflammatory processes and the ROS production, leading to worse motor performances [29].

Taken together, the experimental data suggest the adoption of KD for PD patients in order to restore the bio-energetic balance with potential neuroprotective effects [30], also due to a consistent improvement in L-Dopa absorption [31]. In fact, it has been demonstrated in some animal models that one of the major metabolites,  $\beta$ -hydroxybutyrate, can reduce the substantia nigra neuron loss and increase the oxygen consumption in mitochondria [32,33]. The beneficial effects of KD on mitochondrial activity explains the improvement of patients' scores in Parkinson' disease [30]. In addition, it has been observed that cortical contusions may be decreased in an animal model of cortical injury through therapeutic ketosis [34]. Furthermore, the KD might improve the health status of patients following traumatic brain injury (TBI), as this

clinical condition may lead to epilepsy in some cases [35].

Overall, ketone supplements are currently being developed, and also medical foods and dietary supplements are emerging in order to help keep low blood glucose levels and elevate ketone levels without forcing any dietary restrictions on patients, whom difficult clinical conditions might make hard to follow.

Some old studies [36-38] proved that the mild H<sup>+</sup> load and blood pH physiologically return back to normal ranges as long as ketones are maintained below the value of 10 mM [39]. However, an important concern that arose was that blood pH may transiently decrease during the initial phases of ketosis, which is due to the accumulation of ketone bodies in the bloodstream [40]. This topic is still under discussion and one of the major aspects to consider is the common confusion about the physiological state of nutritional ketosis in the medical community: ketone bodies were previously considered as "toxic metabolites" [30], 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 [41].

### Conflict of Interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers' bureaus, membership, employment, consultancies, stock ownership, or other equity interest, and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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