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Editorial
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The Broad Avenue of Therapeutic Ketosis in Neurodegenerative and Metabolism-Related Pathologies

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Editorial

The Ketogenic Diet (KD) represents a well-known therapeutic option for refractory epilepsy [1], although mechanisms regulating its anticonvulsant effects still remain partially unknown [2].

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, the brain is not capable to obtain significant energy from FFAs, thus hepatic ketogenesis converts them into ketone bodies: β-hydroxybutyrate (BHB) and Acetoacetate (AcAc), while a percentage of AcAc spontaneously decarboxylates to acetone [3]. Recent perspectives about the KD potentials and neuro protective properties strongly support its experimental and clinical application in a wide plethora of different neurological diseases [4]. 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 [5], amyotrophic lateral sclerosis [6], and some types of cancer [7,8].

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) [9].

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. 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 [10].

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 KD [11,12]. In this light, the evident antioxidant properties of the KD may provide a significant neuroprotective effect against a number of neurodegenerative syndromes [13,14].

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 [15].

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 [10].

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 [16], thus facilitating the inflammatory processes and the ROS production, leading to worse motor performances [17].

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 [18], also due to a consistent improvement in L-Dopa absorption [19]. In fact, it has been demonstrated in some animal models that one of the major metabolites, β-hydroxybutyrate, can reduce the substantia nigra neuron loss and increase the oxygen consumption in mitochondria [20,21]. The beneficial effect of KD on

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mitochondrial activity explains the improvement of patients' scores in Parkinson'disease [18]. In addition, it has been observed that cortical contusions may be decreased in an animal model of cortical injury through therapeutic ketosis [22]. 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 [23].

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.

Recently, an important concern that arose was that blood pH may transiently decrease during the initial phases of ketosis (Withrow, 1980). This phenomenon is due to the accumulation of ketone bodies in the bloodstream, although a few studies have proved [24-26] 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 [27].

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 considered as "toxic metabolites" [28], and thus usually caregivers associate the definition of "therapeutic ketosis" with "diabetic keto acidosis", 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 mM and 8 mM [29].

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