

## Ketogenic diet: a nutritional protocol for a non-pharmacological treatment of Alzheimer's disease

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Alzheimer's disease (AD) is a progressively worsening disease that affects specific brain areas involved in spatial memory, short-term memory and has a negative impact on the individual, limiting his ability of independent life. AD remains asymptomatic for a considerable time before cognitive decline becomes clinically evident. For this reason, the establishment of appropriate nutritional protocols, in the early stage, may be more effective than any drug treatments in the fight against this disease. Ketogenic Diet (KD) is a diet high in fat, adequate-proteins and low carbohydrates producing ketone bodies (KBs) (alternative energy source to glucose for the brain). Nowadays, relations between KBs and cerebral A $\beta$  accumulation are not clear. Most studies focus on the neuronal component and forget the vascular component of AD represented by the blood-brain barrier (BBB), located at the cerebral microvessels level. Consequently, it seems essential to focus on the BBB physiology, and in particular on the BBB's functions of the receptors/transporters and enzymes involved in A $\beta$  peptide transport and metabolism, to better understand the influence of a KD on the onset and the evolution of this disease. For 4 weeks, Wild type mice (129SV) were maintained on KD and Control Diet (CD). Glucose and Beta-hydroxybutyrate (BHB) levels were assessed in blood sample. Microvessel fractions were isolated from total brain and qPCR analyses were performed to study expression of transporters, receptors and enzymes involved in amyloid transport and metabolism at the BBB level. KD fed animals showed increased levels of BHB which was accompanied by an increased expression of Monocarboxylate Transporters 1 (MCT1) and Glucose transporter 1 (GLUT1) at the BBB level. There were not changes in the level of Glucose and body weight in these mice. In addition we observed modifications in the expression of some transporters involved in A $\beta$  exchanges such as Low density lipoprotein receptor-related protein 1 (LRP1) and Multidrug resistance-associated protein 1 (MRP1). The expression of A $\beta$  synthesis enzymes remains unchanged, instead an increase for the A $\beta$  degradation enzyme Endothelin Converting Enzyme 1 (ECE1) was observed. These preliminary results show that dietary factors and in particular KD can modulate the expression of some actors implicated in brain A $\beta$  metabolism at the BBB level.

### Keywords

Alzheimer's disease; brain-blood barrier; ketogenic diet.