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KETOGENIC DIET AND NEURODEGENERATIVE DISEASES: A FOCUS ON ALZHEIMER'S DISEASE, PARKINSON'S DISEASE AND AMYOTROFIC LATERAL SCLEROSIS

Bolliri Carlotta[1], Caronni Serena[1], Ferri Valentina[1], Cereda Emanuele[1,2]

[1]Post Graduate University Course in "Diete e Terapie Nutrizionali Chetogeniche: Integratori e Nutraceutici (NutriKeto)" - Dipartimento di Farmacia, University of Salerno, Via Giovanni Paolo II – Fisciano (SA), Italy
[2]Clinical Nutrition and Dietetics Unit, Fondazione IRCCS Policlinico San Matteo, viale Golgi 19,27100 Pavia, Italy

Email address: ferri.v@virgilio.it; bolliricarlotta@gmail.com; serena.caronni@gmail.com; nutriketo@unisa.it

Abstract

Some studies reported that keton bodies could be a more efficient energy source than glucose, even for the brain. After being tested for the from which the ketogenic diet gets first time in 1921 for the treatment of refractory childhood epilepsy the ketogenic diet (KD) has become an interesting and promising alternative approach not only to many neurologic and neuromuscular diseases, but also to all type of diseases called "diseases of progress". The interest has been also increased by the multiple failures collected in drug development studies. . This short review aimed to summarize the available evidence on the use of KD in the three most common neurodegenerative diseases: Alzheimer's disease (AD), Parkinson's disease (PD) and Amyotrophic lateral sclerosis (ALS).Pre-clinical studies are more abundant than clinical ones, although preliminary trails in humans have shown promising results with positive effects on cognitive functions in both AD and PD and motor symptoms in PD. Evidence in ALS is only pre-clinical but a phase-III study is currently ongoing. The major limitations of clinical studies are the low number of patients treated and the short duration of the intervention.

Although a valuable theoretical basis for the use of KDs in neurodegenerative diseases does exist, further studies are warranted before KD can be conveniently and extensively translated into daily clinical practice.

Nonetheless, long-term feasibility and safety concerns on its use in the old patient should be better addressed.

Keywords: *ketogenic diet, neurodegeneration, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Amyotrofic lateral sclerosis, cognitive state.*

Introduction

After being tested for the first time in 1921 for the treatment of pharmaco resistant childhood epilepsy the ketogenic diet (KD) has become an interesting and promising alternative approach - stand-alone metabolic therapy or as part of general, therapeutic strategy - to many neurologic and neuromuscolar diseases (1).

Some studies reported that keton bodies (KBs) could be a more efficient energy source than glucose, even for the brain. They are metabolized faster than glucose and bypass the glycolytic pathway by directly entering the TCA cycle (tricarboxylic acid cycle). Consequently, there is a decrease in ATP generation by glycolysis and an increase in its production by mitochondrial oxidation. Moreover, although both glucose and KBs produce two molecules of acetyl-CoA, glucose reduces four molecules of NAD+ during acetyl-CoA synthesis, while and KBs reduce either one or none (1). For these reasons, KD has a high impact in tissues with a high-energy requirement, such as brain and muscles. Even if the brain represents 2% of one's body weight, it consumes about 20% of the body's energy stores. Similarly, in the resting state, 20% of the energy expenditure is devoted to muscle, and it can largely increase with muscle contractions (1).

KD has been shown to effectively treat or alleviate symptoms of neurological disorders associated with aberrant energy metabolism, such as epilepsy, even in the presence of a persistent molecular pathology (2).

The efficacy of KD in pediatric patients affected by refractory epilepsy has been proven for almost a century, with more than 50% reduction in seizures. Motor function has been shown to be improved by KD in rodent models of Alzheimer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis. These studies have proposed that KD may induce a modification in synaptic morphology and function, involving ionic channels, glutamatergic transmission, or synaptic vesicular cycling machinery. Thus, the effects of KD administration on the neuromuscular system come through different mechanisms. KD can directly induce metabolic shifts due to the high blood levels of KBs and to the restriction of carbohydrate intake. It can also modify nutrient-integrating pathways, such as the mTOR pathway, involved in autophagy and mitophagy-related mitochondrial renewal. Finally, KD might have potential, indirect roles, such as effects on neurotransmission, oxidative stress, and inflammatory mechanisms. However, little is understood about the molecular mechanisms underlying the impact of KD on motor function and the perspectives of its use to acquire the neuromuscular effects (1).

Ketogenic diet in Alzheimer's Disease

AD is one of the common causes of dementia affecting approximately 24 million people worldwide. It is associated with memory deficiency, decline in language and visuospatial abilities. Despite years of research, the etiology of AD remains unknown, with no available treatment or proven preventative interventions (4). Pathologically, AD is characterized by the progressive accumulation of neuritic plaques of amyloid-beta (Aβ), followed by neurofibrillary tangles of hyperphosphorylated tau (5). Genetically, apolipoprotein E (APOE) alleles (ε2, ε3 and ε4) carry different risks for developing AD: the ε4 allele is associated with major risk compared with ε3 allele; the ε2 allele is related to decreased risk (6).

Some studies carried out on animal model of AD, show possible positive effect of a KD. In these studies KD and the administration of ketone body esters, reduced volumes of accumulation of Aβ (in homogenates of murine brains), and improved cognitive function (7).

Several mechanisms of action of KD, such as reduction of neuronal hyperexcitability, enhancement of mitochondrial metabolism and reduced oxidative stress, could also be a modulator of AD pathological processes, including amyloid aggregation and tau hyperphosphorylation (8).

Impaired glucose metabolism in the brain may be one of the earliest hallmarks of AD and studies carried out on young adults with a high genetic risk for AD, have shown that glucose metabolism alteration could anticipate the onset of pathology, decades before the appearance of dementia (9). Patients affected by AD show impaired glucose

utilization in the hippocampus, posterior cingulate, precuneus and prefrontal locations by positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) (10). The presence of insulin resistance in the brains of AD patients has also been suggested (11). Indeed, the main energy substrate for the brain is glucose, but it has been proposed that KBs, could provide supplementary energy to the brain, with an improvement of mitochondrial efficiency and cognitive function. This metabolic pathway involves β-hydroxybutyrate and acetoacetate, and allow to bypass glycolysis to produce acetyl coenzyme A for the Kreb's cycle (12).

In their study, Reger et al. (13) gave 20 patients a drink either containing emulsified MCTs or a placebo drink and observed a significant increase in serum β-hydroxybutyrate 90 minutes after treatment. The elevation of plasma ketone body was associated with an improvement in Alzheimer Assessment Scale-Cognitive Subscale (ADAS-cog) in ε4- subjects but not in ε4+ patients.

Similarly, Henderson et al. (14) administered MCTs to patients affected by mild or moderate AD, in a randomized, placebo-controlled and double-blinded study. The patients received one dose (10 g of MCTs) during the first 7 day, then two doses (20 g of MCTs) from day 8 to day 90. Also in this study, the administration of MCTs lead to an increase of plasma ketone bodies and to an improvement of cognitive function (evaluated with ADAS-cog). Again, the positive effect was evaluable in ε4- subjects but not in ε4+ patients.

Ota et al. conducted two different studies. In the first one, they reported that a single dose of an MCT-based ketogenic formula had a positive effect on working memory and visual attention in non-demented elderly individuals (5). In the following one, they examined the possible effect of a single chronic administration (12 weeks) of this ketogenic formula to patients with mild or moderate AD (10). After 8 weeks the patients showed a significant improvement in logical memory tests compared to baseline. After 12 weeks they showed a significant improvement in the digit-symbol coding test and immediate logical memory tests.

Seneff et al. (5) proposed a cascade effect to connect the role of the ApoE gene and carbohydrate intake in AD patients. When blood glucose level is high - as during a high-carbohydrate diet- glucose can damage important proteins, such as ApoE with the mechanism of glycation, transforming them in AGEs (Advance Glycation End-products). This damaged ApoE impairs its ability to transport lipids to astrocytes, leading to oxidative stress and mitochondrial dysfunction. ApoE proteins transcribed and translated from ε4 variant of the gene, are more susceptible to glycation. This may explain also the results of Henderson et al. and Reger et al.

Furthermore, there is a clear evidence that AD is related to chronic inflammation in central and peripheral nervous system, and some researchers have hypothesized a role for microbiome in the etiology of AD. Infact they found in AD patients a greater abundance of pro-inflammatory bacterial taxa (for example Proteobacteria) along with low anti-inflammatory taxa (6). Nagpal et al. have recently published a cross-over study in which 17 participants were randomly assigned to either a modified mediterranean-ketogenic diet (MMKD) or an American Heart Association Diet (AHAD) for 6 weeks, followed by 6 weeks of washout and then by 6 weeks of the second diet. Researchers have analyzed cerebrospinal fluid, blood and stool samples at baseline of diet 1, at the end of diet 1, at baseline of diet 2 and finally at the end of diet 2. In AD patients it has been found the expected pro-inflammatory pattern of dysbiosis (the opposite condition of eubiosis). Although there were no significant differences in the α- and β-diversity after MMKD or AHAD, several bacterial phyla, families and genera have shown different changes after the two type of diet. For example the phylum Actinobacteria, family Bifidobacteriaceae and genus Bifidobacterium were significantly decreased after MMKD. In the fecal sample collected after MMKD there was also a lower amount of lactate and acetate. In addition, MMKD have caused a slight increase in the beneficial SCFAs including butyrate.

Ketogenic Diet in Parkinson's Disease

Nowadays all the metabolic, neurodegenerative, cardiovascular, inflammatory, neurological psychic

and oncological diseases are called diseases of progress.

Also Parkinson's disease may be considered (PD) the second chronic neurodegenerative disease of progress. The pathogenesis remains unknown but numerous studies suggest that the primary cause is the degeneration of dopaminergic neurons in substantia nigra, leading to several motor (bradykinesia, resting tremor, curved posture, postural instability) and non-motor symptoms (dysphagia, gastric dysnsfunction cognitive disorders, constipation) (14).

The increase in KBs during a KD has been found to exert neuroprotective effects in animal-model and in-vitro experiments using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP to induce the death of dopaminergic cells substantia nigra (15). The effect of ketone bodies could result from an antioxidant activity, improved ATP synthesis and mitochondrial function.

Philipps et al. (16) presented the results of a pilot, blinded-observer randomized study which compared a ketogenic diet with a low fat diet among PD patients (n=47). Total calorie and protein content of the diets were kept the same: Ketogenic diet plan provided 1750 kcal per day of 152g of fat, 75g of protein,16g of carbohydrate and 11g of fiber; the low fat diet 1750 kcal per day with 42g of fat, 75g of protein. 245 g carbohydrate and 33g of fiber.

Although at baseline, patients assigned to the KD were slightly older (mean age, 64.29 years, vs 61.48 years) and had a slightly more severe disease (mean Hoehn and Yahr score, 2.13 vs 1.78), and symptoms (MDS-UPDRS Parts 1-4)(MDS-UPDRS is a validated rating scale with high internal consistency in measuring motor and nonmotor symptoms in PD) UPDRS scores were significantly decreased in both groups at the end of the intervention. However, in the patients who consumed ketogenic diet, there was a greater decrease in scores on Part 1 (nonmotor daily living experiences) than those who consumed the low fat diet: -4.58 ± 2.17 points (41% improvement) vs 0.99 ± 3.63 points (11% improvement) (P<.001).

The study showed that maintaining a low-fat or ketogenic diet for 8 weeks was both plausible and safe. Both groups lost weight over the course of the study. The observed effects on MDS-UPDRS scores could not be attributed to weight loss and increased dopaminergic drugs availability, because the amount of weight loss was comparable in both study arms.

Also in the clinical study conducted by Vanitallie(17)et al., all PD patients showed an improvement in their symptoms and the score of MDS-UPDRS was reduced by 43% after 28 days of KD.

Krikorian et al. (18) enrolled patients with mild cognitive impairment associated with Parkinson's disease in an eight-week cross-over nutritional intervention with random assignment to a high-carbohydrate Western dietary pattern (n=7) or a low-carbohydrate, ketogenic regimen (n=7). The low-carbohydrate group exhibited improved performances on the lexical access composite. Ketogenesis was found to improve also performances in aspects of executive ability and memory in PD-MCI participants. Perhaps, ketone metabolism may have beneficial effects on medial temporal lobe structures including hippocampus (19). A disease-specific limitation of KD's use in PD patients, could be that the ketogenic diet could interfere with the Levodopa's absorption in bowel.

Ketogenic diet in Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease, is the most common adult-onset neurodegenerative disorder with a lifetime risk of 1 in 2000 and a worldwide incidence of 1-3 new cases per 100,000 individuals (2). It is characterized by a progressive degeneration of spinal and cortical motor neurons, leading to relentlessly weakness and loss of skeletal muscles throughout the body (1, 21). Typical clinical features of ALS are spasticity, limb paralysis, hyperreflexia, generalized weakness, fasciculations, muscle atrophy, dysphagia, dysarthria, shortness of breath, and respiratory failure (21, 22). Besides motor neuron degeneration, ALS is associated with impaired energy metabolism, which is pathophysiologically linked to mitochondrial dysfunction and glutamate excitotoxicity. Ultimately, this leads to death within 3-5 years of onset, most commonly due to respiratory paralysis (2).

The causes of ALS are complex and multifactorial, embracing genetic and environmental factors, and they are poorly understood. Many molecular mechanisms are involved in the pathophysiology, but the starting point of the disease remains unclear. Regardless of the type of ALS, patients exhibit neuronal cell death, which may be caused by excess glutamate and oxidative stress-induced metabolic dysfunction (2). Loss of oxidative control, proteinopathy, generation of excessive oxidative free radicals, neurofilament accumulation, glutaminergic dysregulation, metabolic dysregulation, excitotoxicity and mitochondrial membrane dysfunction are some of the supposed causes. Moreover, decreased mitochondrial complex I activity has been measured in skeletal muscle and spinal cord of ALS patients (15). Apoptosis is thought to be the mechanism of cell death (23). These disrupted cellular functions represent discrete targets for therapies that may ameliorate disease progression (2).

At the moment, drug development has yielded few successes and there is no cure or effective treatment for ALS (2). The only US FDA approved pharmacological therapy is limited to riluzole that causes only a modest decrease of the disease progression and increases survival of only 2 to 3 months (21). The prognosis has not changed dramatically since the first reports, nearly 150 years ago (1).

Researchers have found that the survival of ALS patients is related to several factors, including clinical phenotype, age at onset, sex, early presence of respiratory failure, and treatment with riluzole (22).

ALS could be also caused by an energy imbalance, which is a common phenomenon in SOD1 transgenic mice as well as ALS patients. As in other neurodegenerative disorders, mitochondria may play a critical role in this mechanism and is perhaps a target for the mutant SOD1 protein. Decreased mitochondrial complex I activity has been measured in platelets, biopsied muscle and in the spinal cord of ALS patients. In cultured neurons, treated with pharmacologic agents blocking complex I, an addition of KBs was found to restore the function of this complex (21,23,24). Because of the ability of ketones to alter mitochondrial function and the critical role mitochondria may play in neuronal cell death, researchers have studied the clinical and biologic effects of a ketogenic diet in the SOD1 transgenic mice model of ALS (23). In 2006, Zhao et al. reported the first study showing that diet, specifically a KD, is able to alter the progression of the clinical and biological manifestations of the SOD1 transgenic mouse model of ALS. They noticed that KD-fed mice maintained motor function longer than SOD1-mutant mice fed a standard diet and had more intact motor neurons in the lumbar spinal cord (15). These effects may be due to the ability of ketone bodies to promote ATP synthesis and bypass inhibition of complex I in the mitochondrial respiratory chain (23). They also demonstrated that β-hydroxybutyrate prevented rotenone-mediated inhibition of mitochondrial Complex I.

Regarding studies on ALS mouse models, Siva (24) proposed KD as a promising strategy to slow down the progression of ALS, especially through the increase in mitochondrial function.

In 2012, Zhao et al. (25) confirmed the promising therapeutic approach by way of improvement in mitochondrial function and motor neuron count in ALS mouse model following administration of caprylic acid, a MCT precursor of KBs (1,15). Results show that a KD or caprylic triglyceride stalls the impairment of motor function and reduces death of motor neurons in the spinal cord of transgenic ALS mice by restoring energy metabolism through KBs utilization. KBs can act on mitochondrial function, restoring, for example, complex I function, after a pharmacological blocking (22).

These studies provide experimental evidence showing that prophylactic treatment with a KD may slow motor deterioration and protect motor neurons through a promoting energy production in the mitochondria. The neuroprotective effect due to ketone bodies provides a new approach to potential treatment for ALS through a dietary intervention (23). A phase III clinical trial, evaluating the safety, tolerance and efficacy of KD in ALS patients fed through a gastrostomy tube, has been conducted in the United States, but results have not yet been published (1).

Conclusions

This short review aimed to summarize the available evidence on the use of KD in neurodegenerative disease. KD could be an interesting therapeutic strategy in AD patients, as it could improve and support cognitive function and probably reduce the pro-inflammatory state. In PD patients KD was found to have a positive effect on non-motor symptoms and cognitive functions. Finally, although preliminary evidence is substantially based on animal models, available data indicate that KD could be beneficial to ALS patients.
Although these studies provide a valuable theoretical basis for the use of KDs in neurodegenerative diseases, several important hurdles remain before these findings can be conveniently and extensively translated into daily clinical practice. The major limitations of current evidence are the low number of patients treated and the short duration of the intervention.
Indeed, there are still some concerns on the long-term use of KDs, particularly in the old patient, such as the high risk for malnutrition and nutrients deficiencies, the difficulties in meals preparation and consumption due to disability, as well as the potential adverse effects associated with their use both in the short (e.g. hunger, headache, nausea, vomiting, constipation, and anorexia) and the long-term (e.g. reduced mineral bone density, nephrolithiasis, cardiomyopathy, impaired hepatic functions, anemia and constipation or enhanced atherosclerosis). Further studies are clearly warranted.

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