December 30, 2020

PharmacologyOnLine

Special issue • 2020 • vol.3 • 188-192

ROLE OF THE KETOGENIC DIET IN ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE

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Abstract

Alzheimer's disease (AD) and Parkinson's disease (PD) are the most popular aging associated disease and they are characterized by deposits of neurotoxic misfolded proteins. They are highly complex, due to their multifactorial origin, not only depending on genetic but also on environmental factors.

Therefore, recent studies suggest a neuroprotective role of the ketogenic diet in the prevention and treatment of AD and PD.

The aim of this review is to examine recent literature about this topic (2016-2020).

Keywords: *Alzheimer's disease, Parkinson's disease, ketogenic diet, neuroprotection, ketone bodies, Beta-hydroxybutyrate.*

Introduction

Ketogenic diet consists of oral assumption of a very high fat content (90%), few carbohydrates (8%) and normal protein content (7%).

Since 100 years it has been used as nonpharmacologic mechanism to control refractory epilepsy in children and over time it was studied in other medical conditions, including neurodegenerative diseases (Alzheimer's disease and Parkinson's disease).

The carbohydrate restriction of a KD prevents post-prandial rise in circulating insulin and increases circulating fatty acids that are converted into ketone bodies. In fact, ketogenic diet increases the production of ketone bodies (β-hydroxybutirrate, acetoacetate and acetone) into liver mitochondria, and the former two bypass the blood-brain barrier and are oxidized, reaching higher levels of ATP (Adenosine Triphosphate) than in glucose. Moreover, it was observed in research on rats an increasing activity of glutathione peroxidase in the hippocampus (1). So, because of these antioxidant properties, it has been suggested a neuroprotective effect. Caloric restriction has itself antiinflammatory effects reducing levels of inflammatory mediators such as NFkB, interleukins, TNFα and inhibiting cyclooxygenase -2 (COX-2) and inducible nitric oxide synthase (iNOS)(2).

Medium chain triglycerides (MCT), main constituents of coconut and palm kernel oils, are more efficiently hydrolized into fatty acids and converted into ketone bodies than Long chain triglicerides (LCT). In clinical studies, modified MCT diet has been experimented in order to take under control the symptoms of Alzheimer's disease.

Alzheimer's disease (AD) is one of the most common causes of dementia, and is associated with progressive decline in memory, language and visuospatial abilities as a result of progressive accumulation of neuritic plaques of amyloid-beta followed by neurofibrillary tangles of hyperphosphorylated tau. The etiology of AD is still elusive and no cure has been found. The prevention based on adoption of an healthy lifestyle plays an important role in the occurence of the pathology.

Parkinson's disease is an age-related degenerative disorder of certain brain cells. It mainly affects movements of the body (tremors, shakiness, muscle stiffness, stooped posture) and mental functions including memory and ability to pay attention. It is characterized by abnormal microscopic deposits of alfa-sinuclein, a protein involved in neurotransmission and in neurodegeneration of Dopamine neurons in substantia nigra.

Also in this case, the therapy is still not risolutive.

Few studies have evaluated the role of ketogenic diet in the prevention and treatment of Parkinson's disease (PD) and Alzheimer's disease (AD). The goal of this paper is to review recent literature about the neuroprotective role of the ketogenic diet in both neurodegenerative diseases.

Methods

A review of the most recent and relevant clinical studies about this topic (2016-2020) was performed. The following keywords "alzheimer's disease and ketogenic diet" and "parkinson's disease and ketogenic diet" were used on Google Scholar and Scopus databases.

Results and discussion

Alzheimer's disease. Taylor et al. conducted a clinical study in which the feasibility and the efficacy of the KD were displayed on very mild and mild AD patients. 15 enrolled patients with very mild to moderate AD, received a medium-chain triglyceride–supplemented ketogenic diet for three months followed by a 1-month washout. 10 out of 15 were compliant and during the diet, they achieved a medium improvement of 4.1 points at Alzheimer's Disease Assessment Scale-cognitive score (ADAS-cog). After the 1-month washout, the improvement was reverted to baseline. The results were referred to patients with very mild and mild AD because none of moderate AD had completed the treatment (3).

Ota et al. examined the effect of an MCT-based ketogenic formula on cognitive performance of patients with mild-to-moderate AD in acute and in chronic administration. Two subsequent trials were

performed. In the first trial the effects of a single administration of ketogenic formula on cognitive function was evaluated, followed by a second longitudinal open-label 12-week trial. 20 Japanese patients received a ketogenic formula with emulsified MCTs (Ketonformula) or placebo. The results of this study found out that there were no significant differences between cognitive test scores after a single administration of a ketogenic formula. Instead, in the second trial, significant improvements cognitive functions were registered in patients for a longer period of time, specifically at 8 week and after 12 weeks (4).

According to Nagpal et al., the gut microbiome could be considered as a novel biomarker for detecting mild cognitive impairment and a modified Mediterranean-ketogenic diet (MMKD)could influence the gut microbiome. The randomized, double-blind, cross-over, single-center study enrolled 11 participants with mild cognitive impairment and 6 without any altered cognitive performance. They underwent MMKD and American Heart Association Diet (AHAD) intervention for 6-weeks separated by 6-weeks washout periods. Gut microbiome and several biomarkers were evaluated at before and after diet interventions. At baseline, in mild cognitive impairment subjects, *Proteobacteria* correlate positively with Aβ-42: Aβ-40. Six weeks of MMKD and AHAD demonstrated significant changes at family and genus level. In particular, families *Enterobacteriaceae*, *Akkermansia*, *Slackia*, *Christensenellaceae* and *Erysipelotriaceae* increases while that of *Bifidobacterium* and *Lachnobacterium* reduces on MMKD. The PICRUS (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States) tool-inferred reveal that MMKD but not AHAD decreases the abundance of gene families annotated to the Alzheimer's disease (5).

The study of Neth et al. confirmed neuroprotective role of a ketogenic diet in AD. A Modified Mediterranean-Ketogenic Diet (MMKD) and an American Heart Association Diet (AHAD) were administered to 20 participants with subjective memory complaints (n = 11) or mild cognitive impairment (n = 9). The beneficial effects of MMKD were correlated to a significative increasing of Aβ42 protein and decreasing of tau proteins. Furthermore, the cerebral perfusion and ketone body uptake were enhanced. No significative differences in terms of improved memory performance were detected in both diets (6).

Torosyan et al performed a randomized clinical trial in which caprylidene, the medium-chain triglyceride of caprylic acid was administered to 16 patients with mild-to-moderate AD. They underwent PET scans in order to examine regional cerebral blood flow (rCBF). Only the subjects lacking ε4 allele negative had significantly elevated rCBF in the left superior lateral temporal cortex after adopting a caprylidene diet for 45 days (7).

Croteau et al. carried out a study in which mild-moderate AD patients consumed 30 g/d of two different MCT supplements for one month. Brain ketone (11C-acetoacetate) and glucose (FDG) uptake were evaluated by PET at baseline and after each MCT intervention. Both types of MCT increased total brain energy metabolism by increasing ketone uptake without influencing brain glucose utilization (8).

Fortier et al. validated the results of the previous study (8) through the BENEFIC trial. This latter had as primary and secondary outcomes the assessment of brain glucose metabolism and cognitive performance (baseline vs 6 months later). Primary endpoints were positron emission tomography (PET), magnetic resonance imaging (MRI). Secondary endpoints were MMSE and MoCA. 52 enrolled patients with MCI were blindly randomized to 30 g/day of ketogenic medium chain triglycerides (kMCTs) or placebo. At the end of study, plasma concentrations of Acetoacetate and Beta-Hydroxybutyrate increased of 221% and 262%, respectively in the group with kMCTs. No differences were shown in the placebo group. The cerebral metabolic rates of glucose were unchanged in either group (9).

Parkinson's disease. Phillips et al. conducted a randomized, controlled trial to compare the plausibility, efficacy and safety of a low-fat, high-carbohydrate diet versus a ketogenic diet. 59 enrolled patients met the following inclusion criteria (age between 40-75 years, diagnosis of PD, MoCA (Montreal Cognitive Assessment) score >20, BMI

(Body Mass Index) > 18,5) and 47 were randomized to low-fat diet group and ketogenic diet group. The patients were followed up for 8 weeks. During each visit, at baseline and at week 8, changes in Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), weight, BMI, HbA1C, triglycerides, HDL, LDL, total cholesterol, Urate, CRP were measured. Ketogenic diet group showed a significant decreased score for nonmotor daily living experiences. There were no between-group differences in decreased scores for motor daily living experiences, motor examination and motor complications. There were notable between-group differences observed for HDL, LDL, total cholesterol, urate and in fact, these parameters were significantly increased in ketogenic diet group. The most common adverse effects were excessive hunger in low-fat group and intermittent exacerbation of the PD tremor and/or rigidity in ketogenic group (10).

Koyuncu et al investigated the effects of a KD on voice quality (VQ). 74 patients with PD, affected by voice disorder PD-related were enrolled to the study in which they were randomized in two groups (regular diet vs ketogenic diet). The voice quality was assessed by Voice Handicap Index (VHI) before and 3 months after diet. The results of the study were reported for 68 out of 74 PD patients who completed the study. After the diet, all mean VHI parameters were improved in KD group (11).

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