PERSPECTIVE

To treat or not to treat Alzheimer's disease by the ketogenic diet? That is the question

Alzheimer's disease (AD) and current treatments: AD is a serious neurological disorder worldwide that affects about 26 million people, and whose prevalence has been calculated to quadruple by 2050, thus reaching over 1% of the total population, with the highest prevalence occurring in both adults and elderly (Pluta et al., 2018). Neurodegenerative processes of the sporadic form of AD probably start 20 years before the clinical onset of the disorder (Pluta et al., 2018). This disease is the most important cause of dementia in world aged society (~75%). AD is a disorder that affects not only patients but also their caregivers. The social and economic burden associated with AD was calculated as an example in the United States alone; 600 billion dollars annually is spent on caring for AD patients (Pluta et al., 2018). AD is the one of the great health-care challenges of the 21st century. The incidence of AD, a chronic and progressive neurodegenerative disorder, is increasing, as well as the need for efficient methods of diagnosis, prevention and treatment (Pluta et al., 2018). The characteristic clinical and neuropathological hallmarks of AD are: dementia as the main clinical symptom and in post-mortem neuropathological examination, the presence of amyloid plaques as well as neurofibrillary tangles and loss of neurons in the brain of AD patients. The role of amyloid and tau protein is questioned in the etiology of AD and other causes such as ischemic etiology are being considered (Pluta and Ułamek-Kozioł, 2019). There are several treatments that are not causal but symptomatic that are not effective, especially for advanced disease. To date, only a few drugs are approved, such as acetylcholinesterase inhibitors and memantine. Drugs that regulate partly the activity of neurotransmitters and partly alleviate behavioral symptoms. Other treatment options include active and passive immunization, anti-aggregation specifics, and secretase inhibitors. The road to clarity AD etiology, early final ante mortem diagnosis and treatment has been one fraught with a wide range of complications and numerous revisions with a lack of a final solution. Research has recently been launched to identify new mechanisms underlying AD that could be the target of new prevention strategies (Pluta and Ułamek-Kozioł, 2019). Therefore, other treatment options can be recommended, and the ketogenic diet seems to be an interesting last resort solution at the moment (Rusek et al., 2019). The diet contains large amounts of fat and low carbohydrates with vitamin supplementation. New scientific articles suggest that a low-carbohydrate and high-fat ketogenic diet may help alleviate the brain damage in AD (Ota et al., 2019; Rusek et al., 2019). A ketogenic diet can alleviate the effects of impaired glucose metabolism in AD by providing ketones as an additional source of energy. Here, based on new data, we have presented that a ketogenic diet can be effective in preventing and treating AD, but both ketone bodies production and carbohydrate reduction are needed to achieve this.

Ketogenic diet: The ketogenic diet assumes a diet with a very high fat and low carbohydrate content, reducing carbohydrates to less than 10% of the energy consumed. This restriction triggers the transition from glucose metabolism to fatty acid metabolism, resulting in the formation of ketone bodies, such as acetoacetate and beta-hydroxybutyrate, as energy substrates. A ketogenic diet provides enough protein for growth and development, but not enough carbohydrates for metabolic needs. So energy comes mainly from both dietary fat and from patient own fat. The ketogenic diet is a biochemical fast that encourages organs to use ketone bodies as the main source of fuel to replace glucose in the brain.

Ketogenic diet *versus* amyloid and tau protein: This diet lowered total amyloid level and reduced amyloid plaque buildup in the brain, while reversing amyloid toxicity (Broom et al., 2019). Ketogenic diet treatment has been found to reduce levels of soluble beta-amyloid peptide 1–40 and 1–42 while increasing the intracellular domain of the amyloid protein precursor in the brain of a mouse model of AD and reverses amyloid toxicity (Kashiwaya et al., 2013). In contrast, other observations have shown that this diet enhances amyloid accumulation in the brains of transgenic mice (Rusek et al., 2019). Consumption of the ketogenic diet for 43 days by transgenic mice caused a 25% decrease in soluble β-amyloid peptide 1–40 and 1–42 in brain homogenates, but did not affect the task of recognizing the object (Rusek et al., 2019). The ketogenic diet has properties to reduce the pathology of the amyloid and tau protein in a mouse model of AD (Kashiwaya et al., 2013). This was observed in an immunohistochemical study that revealed reduced amyloid accumulation and deposition of hyperphosphorylated tau protein in the subiculum, CA1 and CA3 areas of the hippocampus, amygdala and brain cortex (Kashiwaya et al., 2013) (**Figure 1**).

Ketogenic diet *versus* dementia: It has been noted that ketone can improve proteopathic and behavioral deficits in the mouse model of AD (Kashiwaya et al., 2013). Ketogenic diet also improves motor performance but does not influence amyloid levels and cognition in a mouse model of AD (Rusek et al., 2019). In old rats, taking ketogenic diet for more than three weeks improved learning skills and memory. This has been associated with increased angiogenesis and capillary density, suggesting that a ketogenic diet may support cognitive function through the development of a vascular network (Rusek et al., 2019). Several pilot studies in patients with AD have shown that supplementation with ketogenic diet improves cognitive function, verbal memory, mood, affect, self-care, daily activities, visual attention and working memory (Taylor et al., 2017; Ota et al., 2019; Rusek et al., 2019). Daily intake of caprylidene for 45 days in a randomized, double-blind pilot study resulted in increased cerebral blood flow in specific brain areas in AD patients without the 4 apolipoprotein E allele. In addition, an increase in brain ketone bodies level was noted during treatment as shown in PET ^{11}C acetoacetate imaging, this fact was observed in patients with mild to moderate AD after taking a ketogenic diet for one month (Rusek et al., 2019). In an acute single placebo-controlled study, plasma ketone bodies level increased after ingesting the ketogenic diet, but no changes in cognitive test scores were observed (Ota et al., 2019). However, in another open-label chronic study by above authors, the ketogenic diet had a significant impact on improving cognitive function in AD patients, despite the fact that the increase in ketone bodies level in the body was not statistically significant. To our knowledge, this is the first study to investigate the effects of acute single and chronic continuous use of a ketogenic diet in the same patients (Ota et al., 2019). Although the authors were unable to demonstrate the acute effect of the ketogenic diet on any cognitive function, but it was noticed that chronic consumption (2–3 months) of the ketogenic diet has a positive effect on working memory, short-term memory and processing speed in patients with mild to moderate AD. However, the results should be interpreted cautiously because the study was limited by a small group and a single-arm (no placebo group) design measuring the chronic effect (Ota et al., 2019) (**Figure 1**).

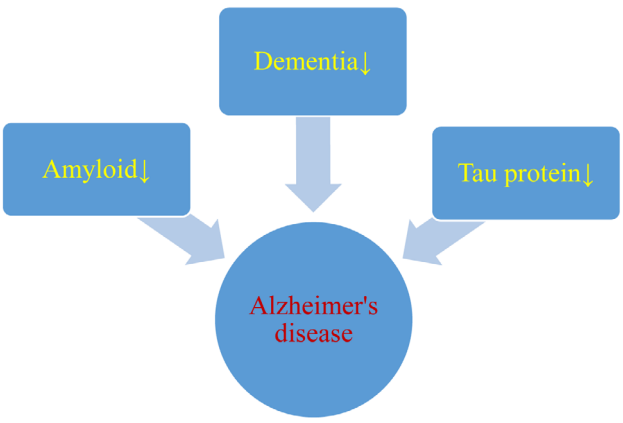

Figure 1 The likely effect of a ketogenic diet on hallmarks of Alzheimer's disease.
↓: Decrease.

Possible mechanisms of the ketogenic diet: It has been shown that diet can inhibit gamma-aminobutyric acid degradation (Barzegar et al., 2019). Studies in rats have shown that diet can increase agmatine level in the hippocampus and is likely to inhibit various brain-stimulating receptors, including N-methyl-D-aspartate, histamine and adrenaline receptors (Calderón et al., 2017). It has been noted that monoamine neurotransmitters, including noradrenaline, dopamine and serotonin, are positively influenced by diet (Barzegar et al., 2019). It is suggested that the negative consequences of excitotoxicity and apoptosis mechanisms can be improved by means of a ketogenic diet (Rusek et al., 2019). It has been shown that the ketogenic diet can regulate calbindin, which has neuroprotective potential due to its ability to buffer intracellular calcium (Barzegar et al., 2019). Other neuroprotective properties of the ketogenic diet may mediate the inhibition of proapoptotic factors such as caspase 3 (Barzegar et al., 2019).

Side effects of the ketogenic diet: A wider use of the ketogenic diet may be limited by the number of early side effects (gastrointestinal disorders, acidosis, hypoglycemia, dehydration and lethargy) and late side effects (hyperuricemia, hyperlipidemia, kidney stones, easy bruising, and reduction in height and weight) (Rusek et al., 2019). Lately, data are available on the negative effect of the ketogenic diet on the quality characteristics of lipoprotein subfraction, indicating an atherogenic phenotype as a new side effect (Ułamek et al., 2016).

Conclusion and future perspective: To date, the results of using the ketogenic diet as a drug obtained in the treatment of neurodegenerative diseases seem to be particularly interesting in order to restore cognitive functions, although their number is limited. The few human studies available to date are based on a pre/post-design, but without a reference control group and no authentic randomization. The results showed causal evidence and underlined the need to increase the number of studies to demonstrate that the ketogenic diet induces cognitive improvement in neurodegenerative diseases. In recent years, the reputation of the ketogenic diet in terms of its therapeutic effects has been growing. In molecular research and partially polemic publications, the ketone diet gives misleading results because this diet has no single target point (Rusek et al., 2019). The authors of these discrepancies obtained their information from the data obtained in high-throughput screening. However, high-throughput screening is susceptible to technical artifacts and is therefore a deceptive tool because potential substances for drug can be omitted. In addition, the fact that the ketogenic diet, like many other natural substances, has more than one drug target, indicates its versatile use and low risk of inducing resistance to treatment. Although justified doubts exist and are crucial as to the reliability of therapeutic results, it makes no sense to disparage everything that has so far been published about the therapeutic effects of the ketogenic diet in the treatment of malignant gliomas, epilepsy or neurodegenerative diseases (Rusek et al., 2019). Instead, we should take the challenge of distinguishing between scientifically substantiated and false therapeutic results; otherwise, we will lose a promising substances for complementary and alternative treatment strategies. Rejecting some of the effects of ketogenic diet treatment would simply be ignorance. Opponents of the ketogenic diet criticize the fact that it has never been demonstrated to be definitely effective in a randomized placebo-controlled clinical trial for any indication (Rusek et al., 2019). Critics should consider the fact that it is almost impossible to get financial support for conducting a clinical trial with a substance that cannot be patented and is therefore not economically interesting. Another point to consider is the study design, the ketogenic diet cannot be tested in randomized placebo-controlled studies because currently clinical trials are conducted as test substance against standard therapy, otherwise the study will not be approved by the ethics committee. Therefore, the question is against which drug currently used to treat AD should we test the ketogenic diet? There is no doubt that due to comprehensive data from preclinical studies, along with the first results of individual patients or small cohorts (Rusek et al., 2019), the next task must be to test ketogenic diet in well-designed clinical trials. However, the biggest challenge will be finding sponsors for clinical trials on ketogenic diet as this promising diet cannot be exploited economically. Further double-blind investigations are needed to clarify the effectiveness of taking the ketogenic diet. In summary, future studies should focus on the correct identification of patients (in terms of age, type and duration of AD, comorbidities, and Apo E 4 allele$^{+/-}$) and they are necessary to answer the question in the title.

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Marzena Ułamek-Kozioł, Ryszard Pluta*
Laboratory of Ischemic and Neurodegenerative Brain Research, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland (Ułamek-Kozioł M, Pluta R)
First Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland (Ułamek-Kozioł M)
***Correspondence to:** Ryszard Pluta, MD, PhD, pluta@imdik.pan.pl.*
***orcid:** 0000-0003-0764-1356 (Ryszard Pluta)*
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