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THE IMPACT OF THE KETOGENIC DIET ON THE HEALTH OF PATIENTS WITH ALZHEIMER'S DISEASE

Julia Samborska

SPZOZ Okręgowy Szpital Kolejowy w Katowicach

julia.samborska.med@gmail.com

https://orcid.org/0009-0001-2157-7015

Paweł Więckowiak

Śląski Uniwersytet Medyczny w Katowicach

pawew36@gmail.com

https://orcid.org/0009-0004-6610-1792

Karina Stelmaszak

SPZOZ Okręgowy Szpital Kolejowy w Katowicach

stelmaszak1259@gmail.com

https://orcid.org/0009-0006-3877-2753

Katarzyna Stencel

Specjalistyczny Zakład Opieki Zdrowotnej "MULTIMED" Sp. zoo

katarzynastencel96@gmail.com

https://orcid.org/0009-0006-9574-9277

Aleksandra Ogiegło-Kowalczyk

SPZOZ Okręgowy Szpital Kolejowy w Katowicach

aleksandra.ogieglo@gmail.com

https://orcid.org/0009-0008-8773-7123

Monika Wojtasik

Przychodnia Wielospecjalistyczna w Mikołowie

monika.wojtasik95@gmail.com

https://orcid.org/0009-0008-6723-3841

Michał Głodzik

Przychodnia Bracka Bielszowice, Ruda Śląska

glodzikmichal@gmail.com

https://orcid.org/0009-0009-4751-1784

Marek Miśkiewicz

Wojewódzki Szpital Podkarpacki im.Jana Pawła II w Krośnie

miskiewiczkeram@gmail.com

https://orcid.org/0000-0002-3691-343X

Katarzyna Żak

Uniwersyteckie Centrum Kliniczne w Gdańsku

lek.katarzyna.zak@gmail.com

https://orcid.org/0009-0000-7056-1960

Martyna Łęcka
Szpital Murcki Sp z o.o. Katowice, Sokołowskiego 2, 40-749 Katowice
martyna.lecka@gmail.com
https://orcid.org/0009-0007-1473-8400

ABSTRACT:

INTRODUCTION:

Diet is an integral element of every individual's health. Its impact on the functioning of the human body has fascinated scientists for years. One of the diets that alters the mechanism of the body's functioning is the ketogenic diet. The impact of the ketogenic diet on various disorders is still under investigation. It is known to have shown numerous benefits in reducing epileptic seizures, but its impact on other neurological disorders is less known. In this literature review, the efficacy of ketogenic therapies was assessed in Alzheimer's disease.

AIM OF STUDY:

Review of the current literature (since 2018) on the effects of implementing a ketogenic diet in patients with Alzheimer's disease.

MATERIALS AND METHODS:

The review was based on data gathered from the PubMed database using the keywords: 'ketogenic diet in Alzheimer’s disease,' 'ketogenic therapies Alzheimer disease,' and 'ketogenic diet in neurological disease’**.**

SUMMARY:

The ketogenic diet enhances the daily functioning of Alzheimer's patients. It significantly improves their cognitive functions, and changes in brain blood flow are visible in imaging studies. The ketogenic diet also positively modulates the gut microbiome in Alzheimer's

patients. It represents a promising option in combating cognitive symptoms of Alzheimer's disease.

KEY WORDS: Health; Diet; Ketogenic diet; Alzheimer’s disease; Diet in neurological diseases; Nutrition; Ketone bodies;

INTRODUCTION:

Alzheimer's disease is a neurodegenerative brain disorder. It is characterized by the presence of progressive and chronic deficits in at least two domains of cognitive function: attention, memory, language, visuospatial skills, and executive functions. [1]

For the assessment of cognitive functions, screening tests specifically designed for this purpose can be utilized. NICE (National Institute for Health and Care Excellence) recommends the use of the 10-point Cognitive Screen (10-CS), 6-Item Cognitive Impairment Test (6CIT), 6-Item Screener, 6-Item Memory Impairment Screen (MIS), Mini-Cog, or Test Your Memory (TYM) [2]. When interviewing a close relative or informant of an individual suspected of dementia, the consideration of supplementing these tests with structured tools such as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) or the Functional Activities Questionnaire (FAQ) is advised [2].

The ketogenic diet is a high-fat and low-carbohydrate diet (protein intake is adequate to meet requirements) [3]. Its implementation leads to the creation of a metabolic state in the body similar to fasting, resulting in increased production of ketone bodies, namely β-hydroxybutyrate (BHB), acetoacetate (AcC), and acetone [3]. Ketone bodies serve as an energy source for cells in the body, alongside glucose [4]. In neurodegenerative diseases, the absorption, transport, and metabolism of glucose are often impaired. Therefore, a shift from glucose to ketone bodies as an energy source improves mitochondrial function, increases ATP

production, and stabilizes synaptic activity [5, 6]. Ketone bodies also have a modulating effect on inflammatory processes and oxidative stress, as they act as signaling molecules involved in post-translational protein modifications [3]. They activate the transcription factor NRF2 (nuclear factor erythroid 2-related factor 2), leading to the transcription of antioxidant genes [7, 8]. An increase in the production of mitochondrial uncoupling proteins (UCP), hyperacetylation of Foxo3a (forkhead box O3), and Mt2 (metallothionein-2) is also observed due to the action of BHB (inhibitor of histone deacetylases) [9]. All these mechanisms enable the reduction of reactive oxygen species in the body, which can be destructive to the nervous system. The ketogenic diet is also considered promising for its impact on the biosynthesis of GABA, which is an inhibitory neurotransmitter [10].

In Alzheimer's disease, there is a deposition of β-amyloid peptide and accumulation of TAU protein in the cytoplasm of neurons. This leads to neuronal death, decline in cognitive function, and behavioral disturbances [11]. The deposition of β-amyloid and TAU protein is accompanied by the activation of microglia and astrocytes [12]. These cells release pro-inflammatory cytokines and chemokines, causing chronic neuroinflammation. In turn, neuroinflammation promotes neurodegeneration and β-amyloid production [11]. Hyperglycemia is also associated with neuroinflammation, leading to oxidative stress, which may trigger the amyloid cascade in Alzheimer's disease [11]. There is a correlation between high carbohydrate intake and increased deposition of β-amyloid [13]. Alzheimer's disease may also result from insulin resistance, which affects insulin signaling and promotes the deposition of β-amyloid peptide and TAU protein [14]. Additionally, the expression of the apolipoprotein E4 (ApoE4) allele, typical for type 2 diabetes and recognized as a risk factor for Alzheimer's disease, is shared [15].

However, the ketogenic diet has its weaknesses. Its use requires special medical care, as side effects can occur. First, gastrointestinal complaints such as nausea, vomiting and obstruction occur due to excessive fat intake. [26] It should be noted that ketosis has an anorexigenic effect, which can be used to treat obesity, [27] but is not beneficial in patients with neurodegenerative diseases. [26]

RECENT FINDINGS AND RESEARCH GAPS:

The use of fluorodeoxyglucose positron emission tomography (FDG-PET) can visualise abnormal glucose metabolism in the brain, which occurs from the earliest stages in

patients with Alzheimer's disease, but also in asymptomatic individuals at risk of Alzheimer's disease. Areas in the brain with hypometabolism show impaired glucose utilisation, but can still efficiently take up ketone bodies. [16] While the exact reasons for the onset of Alzheimer's disease after the age of 65 are not fully understood, the most significant genetic risk factor identified in this age group is the presence of the ε4 allele of the apolipoprotein E gene (APOE4). [17] In one study using PET scans in patients with Alzheimer's disease, it was shown that daily intake of caprylidene for 45 days was associated with increased blood flow in specific brain areas in patients lacking the E allele of apolipoprotein 4. [17] Another goal was to investigate potential variations in the impact of caprylidene on regional cerebral blood flow (rCBF) between individuals who are positive for the APOE4 allele and those who are negative for it. Individuals who did not possess the ε4 allele showed a noticeable increase in regional cerebral blood flow (rCBF) in the left superior lateral temporal cortex, as determined by the analysis of a specific volume of interest (sVOI), following a 45-day caprylidene diet ($p = 0.04$). This finding was additionally supported by statistical parametric mapping (spm). [17] Statistical parametric mapping (spm) revealed that the anterior cerebellum, left inferior temporal cortex, and hypothalamus exhibited prolonged increases in regional cerebral blood flow (rCBF) in individuals without the ε4 allele. On the contrary, patients carrying the ε4 allele did not demonstrate these alterations in rCBF. [17]

A randomised trial published in 2021 involving 26 patients (21 of whom completed the study) also showed a positive effect of the ketogenic diet on the development of Alzheimer's disease. A baseline assessment was performed in the week prior to the start of the treatment period, followed by assessments at week 6 and 12. Patients' cognitive function and quality of life were assessed. Cognition was assessed using the Addenbrookes Cognitive Examination - III (ACE-III) scale. During the ketogenic diet, patients achieved sustained physiological ketosis (12-week mean beta-hydroxybutyrate level: 0.95 x 0.34 mmol/l). Compared with the usual diet, patients taking the ketogenic diet increased mean within individual ADCS-ADL ((+ 3.13 ± 5.01 points, $P = 0.0067$) and QOL- (+ 3.37 ± 6.86 points, $P = 0.023$). ACE-III also increased, but not significantly (+ 2.12 ± 8.70 points, $P = 0.24$). Changes in cardiovascular risk factors were mostly favourable and side effects were mild. [18] The study concludes that implementing a 12-week modified ketogenic diet in Alzheimer's disease patients seems to result in high rates of retention, adherence, and safety. When compared to a regular diet supplemented with low-fat healthy-eating guidelines, individuals following the ketogenic diet showed enhancements in daily function and quality of life. [18]

It is also worth mentioning a study from 2020. In the entire study, a total of 346 participants were screened, with 26 refusing to participate, and 198 being excluded. Cognitive changes were assessed in a 6-month randomized controlled trial of ketogenic medium-chain triglyceride (kMCT) compared to placebo in mild cognitive impairment (MCI). The kMCT drink improved three domains – executive function, memory, and language: free and cued recall (Trial 1; P = .047), verbal fluency (categories; P = .024), Boston Naming Test (total correct answers; P = .033), the Trail-Making Test (total errors; P = .017). Higher ketones in the serum correlated positively with changes in four cognitive tests. The kMCT group was compared to the placebo group using analysis of covariance, with pre-intervention scores, sex, age, education, and apolipoprotein E4 status considered as covariates. It is noteworthy that this study also observed the metabolic profile in the serum of patients, which did not change after 6 months of kMCT use. This dispels concerns among scientists that the ketogenic diet would negatively impact the lipid profile of patients [19].

In a 12-week study of 16 patients with mild to moderate Alzheimer's disease who were taking a ketogenic formula based on medium-chain triglycerides, significant improvements were observed in the digit-symbol encoding test and immediate logical memory test after prior comparison of cognitive performance before, after four weeks, after eight weeks and after the 12-week study. Significant improvements were also observed in the immediate and delayed logical memory tests after the dietary (WMS-R: post 12 weeks logical memory (immediate) 11.2 ± 11.1, p = 0.001, logical memory (delayed) 6.4 ± 10.2 p = 0.005, digit span and spatial span was not significant; WAIS-III: digit-symbol coding post 12 weeks 44.0 ± 21.6, p = 0.004, the block design was not significant; the Stroop test: strop effect (second) post 12 weeks 94.4 ± 40.6, p = 0.009, correct (numer) was not significant; TMT was not significant). [20] Earlier, the same researchers discovered that a single dose of a medium-chain triglyceride-based ketogenic formula (Ketonformula®) had cognitive-enhancing effects on cognitive functions such as working memory, visual attention, and task switching in older individuals without dementia Regarding cognitive performance, enhancements were noted in the digit span test, Trail-Making Test B, and the overall score ($Z = -2.4$, $p = 0.017$) following the ketogenic meal. The improvement in executive functioning scores showed a positive correlation with the plasma β-hydroxybutyrate level. The cognitive benefits were particularly prominent in individuals with a relatively low baseline global score ($Z = -2.8$, $p = 0.005$), compared to those with a high global score ($Z = -0.7$, $p = 0.51$). [21]

A comprehensive study that examined patients both after the application of a ketogenic diet and after a 1-month washout period was performed. After the ketogenic diet, patients with Alzheimer's showed an average improvement of 4.1 points in ADAS-cog scores ($p = 0,02$). However, after the 1-month washout period, ADAS-cog scores returned to baseline values. The conclusion from this study might be that the positive effects of the ketogenic diet persist only during its application and diminish after discontinuation. In this research, serum β-hydroxybutyrate (BHB) levels exhibited a significant increase at months 1, 2, and 3 in comparison to the baseline values (0.11 mmol/L at baseline vs. 0.52, 0.34, and 0.31 mmol/L; $P < .001$), returning to the normal range by the end of the washout period (0.12 mmol/L). The serum BHB findings generally correlated with urine ketone responses, with the exception of one instance. In this study researchers also compare anthropometric measures, lipid status, serum biomarkers, metabolic status but neither of them was not significant. Only dietary intake of fat (baseline 90.6 g, after 3 months 166.7 g, $p < 0.001$) and carbohydrate (baseline 209.8 g, after 3 months 46.0 g, $p < 0.001$) was significant.[22].

In 2019, researchers investigated whether the gut microbiome of patients with mild cognitive impairment and Alzheimer's disease differs from that of cognitively normal older adults and whether and how the Modified Mediterranean-Ketogenic Diet (MMKD) affects the gut microbiome in relation to Alzheimer's disease biomarkers in cerebrospinal fluid (CSF). Initially, it was demonstrated that individuals with normal cognitive function compared to those with impaired cognitive function do not show significant differences in microbiome diversity. However, surprisingly, several unique microbial signatures were detected in individuals with mild cognitive impairment. The following conclusions were drawn: Proteobacteria positively correlate with Aβ-42: Aβ-40, but fecal propionate and butyrate correlate negatively with Aβ-42 in individuals with mild cognitive impairment. The abundance of Enterobacteriaceae, Akkermansia, Slackia, Christensenellaceae, and Erysipelotriaceae increases, while Bifidobacterium and Lachnobacterium decrease in the MMKD group, and AHAD increases Mollicutes. MMKD slightly reduces fecal lactate and acetate while increasing propionate and butyrate. Conversely, AHAD increases acetate and propionate while reducing butyrate. It appears that specific microorganisms may correlate with mild cognitive impairment. MMKD, on the other hand, may influence the improvement of Alzheimer's disease biomarkers in cerebrospinal fluid by modulating the gut microbiome [23].

In 2023, conclusions were drawn from a fairly large study involving patients with Alzheimer's disease, Parkinson's disease, and moderate cognitive impairment who followed various diets, including the ketogenic diet. The ketogenic diet was used in all studies involving patients with Parkinson's disease and showed significant improvement in patients' balance and motor functions. In the group of patients with Alzheimer's disease and moderate cognitive impairment, various ketogenic therapies were applied, including a ketogenic diet, low-carbohydrate diet, modified Atkins diet, Mediterranean diet with coconut oil supplementation, ketogenic diet with ketogenic medium-chain triglyceride (kMCT) supplementation, as well as ketogenic supplements, including a ketogenic drink with kMCT, oral ketogenic compounds (Axona and AC-1202), and MCT oil or emulsion. The ketogenic diet slightly improved cognitive functions in patients, but this improvement was not statistically significant. The Mediterranean diet, modified Atkins diet, and low-carbohydrate diet showed statistically significant improvements in some cognitive measures. The use of ketogenic supplements, drinks, or compounds showed variable results. Axona and AC-1202 compounds did not show a significant improvement in cognitive functions. Most MCT supplements had a positive impact on cognitive functions when the diet was adhered to [24].

CONCLUSION:

The above results unequivocally indicate a promising positive impact of the ketogenic diet in the therapy of Alzheimer's disease, especially in combating cognitive symptoms. Large-scale randomized controlled trials, including long-term patient observations, are necessary. However, the most significant obstacle will be the potential adverse effects of the diet, including nausea, vomiting, diarrhea, constipation, fatigue, and hunger. [25] These adverse effects can significantly hinder daily functioning and discourage patients from adhering to the ketogenic diet, even despite its long-term positive benefits in combating the disease. Maintaining the diet itself is also challenging, as it requires excluding a significant number of food products with potential beneficial effects on the body. The diet may seem monotonous during prolonged use. Nevertheless, it is worth considering the inclusion of the ketogenic diet in the treatment of patients with Alzheimer's disease, as the benefits far outweigh the potential inconveniences associated with the therapy. [26, 27]

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4. Author contributions:

- Conceptualization: Julia Samborska, Paweł Więckowiak, Aleksandra Ogieło-Kowalczyk, Karina Stelmaszak, Katarzyna Stencel, Marek Miśkiewicz, Monika Wojtasik, Michał Głodzik, Katarzyna Żak, Martyna Łęcka

- Methodology: Julia Samborska, Karina Stelmaszak, Paweł Więckowiak

- Software: Karina Stelmaszak, Monika Wojtasik, Martyna Łęcka

- Formal analysis: Marek Miśkiewicz, Aleksandra Ogieło-Kowalczyk

- Data curation: Karina Stelmaszak, Katarzyna Stencel, Katarzyna Żak, Aleksandra Ogieło-Kowalczyk

- Visualization: Karina Stelmaszak, Katarzyna Stencel, Julia Samborska, Katarzyna Stencel,

- Supervision: Karina Stelmaszak, Michał Głodzik, Marek Miśkiewicz, Monika Wojtasik, Michał Głodzik, Katarzyna Żak, Martyna Łęcka

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