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CLINICAL APPLICATIONS OF KETOGENIC DIET AND MEDIUM CHAIN TRIGLYCERIDE SUPPLEMENTATION IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE

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Abstract

Alzheimer's dementia (AD) is a slowly progressing neurodegenerative disease characterized by progressive cognitive decline, behavioral disturbances, diffuse brain atrophy, impaired neuronal function, brain insulin resistance, and deposits of beta-amyloid plaques and tau protein tangles. AD affects one in every eight persons in the United States over the age of 65 and one in every three people over the age of 80. Conventional medicines slow the progression of the cognitive decline but are unable to stop or reverse the disease. This review aimed to evaluate if ketogenic diet (KD) and medium chain triglyceride (MCT) supplementation caused improvement in cognition when compared to glucose or a high glycemic index diet in patients with mild to moderate AD. There were 15 relevant articles selected from various databases, and the findings were synthesized for clinical practice implications. Based on current clinical evidence, the KD is a great option for adjuvant therapy in the treatment of mild to moderate cognitive impairment in the early stages of AD. This review provides examples of clinical applications of KD and MCT supplementation in the primary care setting as part of dietary counseling. Future research is needed to evaluate the short and long-term use of KD and MCT supplementation and their effects on cognition and progression of AD.

Keywords: Alzheimer's Disease, family nurse practitioner, ketogenic diet, ketone body, medium chain triglyceride, low glycemic load, low carbohydrate diet.

Impact of Alzheimer's Dementia in the United States

Alzheimer's Disease (AD) is a progressive and irreversible neurodegenerative disease characterized by cognitive decline (Alzheimer's Association, 2023). It affects one in eight older adults in the U.S. by 65 years of age and about one in every three adults over the age of 80 (Alzheimer's Association, 2023). The Alzheimer's Association estimates the prevalence of patients with AD at 6.7 million people in 2023 (Alzheimer's Association, 2024). According to the Centers for Disease Control and Prevention (CDC) (2020), AD is a public health crisis affecting over 5 million American adults (Center for Disease Control and Prevention, 2020). The lifetime cost of care for a person with dementia is estimated at $392,874, of which 70% is represented by unpaid caregiving and family caregivers' out-of-pocket expenses for food and medications. The remaining expenses are often Medicare and Medicaid costs (Alzheimer's Association, 2023). AD affects women at higher rates than men, 63% vs. 47%. Also, the majority of caregivers taking care of patients with AD are women, at 73% (Alzheimer's Association, 2023).

One role of the family nurse practitioner (FNP) in managing AD is recognizing the signs and evaluating for cognitive impairment in symptomatic older adult patients. FNPs also promote health to patients with AD and their families, offer appropriate vaccinations, and refer these patients for proper cancer screening (Dunphy et al., 2023). Educating patients with mild to moderate AD and their families regarding healthy diets, making dietary changes to decrease simple sugar and carbohydrate, and increasing protein and healthy fat consumption or supplementation with MCT or KB should be an important part of care for patients with AD to prevent neuroinflammation and its effects on cognition. Furthermore, FNPs occupy strategic

positions and should be tasked with educating their patients regarding AD risk reduction and proactive management of modifiable risk factors such as dietary modifications to delay the onset and severity of AD (World Health Organization, 2019).

Alzheimer's Dementia Pathophysiology and Medical Treatments

AD was first described by Alois Alzheimer, the first psychiatrist to diagnose the disease in 1901 with distinct features (Ellison, 2018). In 1906, Dr. Alzheimer published his description of patients with early onset cognitive decline, paranoia, fear, and aggressivity and linked this psychiatric condition to the brain pathology of amyloid plaque deposits, neurofibrillary tangles, and white matter atrophy, distinguishing this disease from senile dementia (Elison, 2021). Research in the 1970s found that AD manifestations are caused by a deficit of the neurotransmitter acetylcholine, a chemical messenger essential for memory function (Ellison, 2018). Current pharmaceutical treatment focuses on increasing levels of acetylcholine in the brain by either increasing its production or blocking its destruction. However, these agents have mild symptom-reducing effects and cannot slow or prevent disease progression (National Institute of Health, 2023). N-methyl-D-aspartate (NMDA) antagonists can slow the progression of the disease. However, they cannot halt or reverse the degenerative changes of AD or the cognitive decline process associated with the disorder (National Institute of Health, 2023). Reversal or complete cessation of the effects of neuronal degradation has not been achieved with conventional treatments.

Aberrant tau protein accumulation is another hallmark pathological finding in AD (Guo et al., 2017). Healthy tau protein has vital roles in neurons' health and proper functioning, from

DNA synthesis to maintaining structural integrity, axonal transport, and neuro-signaling between neurons (Guo et al., 2017). Unhealthy phosphorylation, which causes structural changes in the tau proteins, can lead to microtubule disintegration, inability to maintain healthy synapses, and impaired neural transmission (Guo et al., 2017).

Relationship of Glucose, Insulin, and Neuroinflammation

The brain makes up about 2% of the body's mass. However, the brain uses 20-25 % of the body's energy, usually 110-140 grams of glucose daily (Jensen et al., 2020). This energy is used to maintain resting potentials, generate action potentials and postsynaptic potentials, regulate presynaptic calcium levels, and recycle neurotransmitters, such as glutamate or acetylcholine. Chronically elevated blood glucose and elevated insulin levels contribute to insulin resistance in the body and brain (Sędzikowska & Szablewski, 2021). Metabolic dysregulation of glucose creates reactive oxygen species (ROS) and causes respiratory chain dysfunction, leading to altered amyloid precursor protein processing, mitochondrial and neuronal cell destruction, and contribute to cognitive decline (Kapogiannis & Avgerinos, 2020). Microglia, cells that support brain cell repair, migrate toward the beta-amyloid plaques and surround them. Microglia also secrete proinflammatory cytokines, including interleukin-1 (IL-1), IL-6, and tumor necrosis factor alfa (TNF)--α), and chemokines, such as Macrophage Inflammatory Proteins-1α (MIP) and (Monocyte chemoattractant protein-1 (MCP-1), that attract astrocytes to envelop the plaques. Many proinflammatory cytokines, IL-6, upregulate APP synthesis and aggregation, accelerating plaque formation and AD progression (Sankar et al., 2020). Other cytokines produce neurotoxic factors, such as nitric oxide, contributing to neuronal death. (Sankar et al.,

2020).

In patients with AD, impaired glucose transport causes neurons to have restricted sources of energy from glucose, decreasing neuronal metabolism and activity (Mullins et al., 2021). In these instances, the brain uses a secondary energy-producing pathway, which uses alternate fuel sources like fatty acids and ketone bodies. Besides providing direct fuel to the mitochondria, these energy substrates decrease inflammation in the brain by reducing excessive production of ROS by the dysfunctional mitochondria (Mullins et al., 2021).

The latest research exploring the pathophysiology of AD points to impaired glucose metabolism and peripheral hyperglycemia as being associated with a higher risk of developing AD (Taylor et al., 2017). Positron emission tomography (PET) metabolism imaging studies demonstrate that hyperglycemia and insulin resistance are associated with impaired glucose metabolism in the brain. Chronic hyperglycemia leads to insulin resistance, which causes glucose hypometabolism, correlating with cerebral amyloid deposition (Taylor et al., 2017). Insulin regulates the metabolism of amyloid precursor protein (APP), which modulates the balance between anabolism and catabolism of amyloid beta (A-beta). Low insulin levels, or the lack of its action in the form of insulin resistance, can result in elevated A-beta levels and accumulation of amyloid plaques in the brain (Sędzikowska & Szablewski, 2021).

Diagnostic Criteria and Assessment Instruments

Diagnosing cognitive impairment can start with an FNP evaluation. Patients with cognitive impairment are brought by their family members with concerns of ongoing memory and critical thinking problems, confusion, and decreased ability to care for themselves at home safely and independently (Dunphy et al., 2023). Diagnostic criteria for AD have been

established by the National Institute on Aging and the Alzheimer's Association (NIA-AA), and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) requires the following:

1. inability or decreased ability to function at work or usual activities
2. decline from a previous level of functioning and performing
3. confusion not explained by delirium or a major psychiatric disorder
4. cognitive impairment from past medical history, in-office mental status examination, or neuropsychological testing of one or more of the following domains: impaired ability to acquire and remember new information, impaired reasoning, inability to handle complex tasks, poor judgment, impaired visuospatial skills, impaired language, changes in personality, behavior or demeanor
5. other core clinical criteria include insidious onset, a history of worsening
6. no evidence of substantial concomitant cerebrovascular (Lewy body, behavioral variant frontotemporal) dementia, primary progressive aphasia, or proof of another neurologic or non-neurologic disease or use of medication affecting cognition (Wolk, 2021).

Quantifying cognitive impairment and staging AD may be completed using one of the multiple cognitive assessment scales in conjunction with clinical judgment. Additionally, research studies often employ a consistent instrument for longitudinal or serial objective measurement of cognition or function. Many scales have a shorter assessment time of 5 minutes, such as Memory Impairment Screen (MIS), Six-Item Screener (SIS), Clock-Drawing Test (CDT), Mini-Cog, and Informant Questionnaires. More detailed scales may take between 5-15 minutes to administer and are used by mood and memory specialists, such as the Mini-Mental

State Examination (MMSE), Montreal Cognitive Assessment (MoCA), or Saint Louis University Mental Status Examination (SLUMS); others may take more than 15 minutes to administer, such as the Addenbrooke's Cognitive Examination (ACE) (Larson, 2022). These screening tools have a sensitivity of 75-92% and a specificity of 81-91%; however, they are not diagnostic in themselves, helping quantify the severity of impairment (Wolk, 2021). Research studies often employ a consistent instrument for longitudinal or serial objective measurement of cognition or function.

Review of the Literature

This literature review and synthesis aim to describe the effects of hyperglycemia, insulin resistance, neuroinflammation, and its adverse impact on cognitive impairment in mild to moderate AD. The guiding PICOT question was: (a) Population: people with mild to moderate Alzheimer's Disease; (b) Intervention: ketone body supplementation in the form of KD, MCT; (c) Comparison: glucose or high glycemic index diet; (d) Outcome: improvement in cognition, slowing of neurocognitive deterioration as evidenced by improved n scores; (e) Time frame: long term: 8-12 weeks to months.

The review's author searched relevant articles using PubMed, CINAHL, Ebscohost, Elsevier, and Sci-hub for relevant, peer-reviewed, published, full-text articles within the last five years, between 2018 and 2023. The article search and review were guided by the chosen keywords: Alzheimer's disease (AD), beta-amyloid, tau protein, insulin, insulin resistance, ketogenic diet (KD), medium chain triglycerides (MCT), fatty acid, memory, cognitive score, glucose, and high glycemic index diet. The chosen articles were also carefully assessed for references. If the reference contained one or more keywords, they were evaluated if they met the

rest of the inclusion criteria.

Inclusion criteria consisted of (a) peer-reviewed research studies; (b) appeared in a professional journal in full text within the last five years since 2018; (c) included many of the keywords, such as Alzheimer's disease, ketogenic diet, or ketone body. Exclusion criteria consisted of (a) no key phrases or (b) only one key phrase, such as Alzheimer's but no ketogenic diet or ketone body.

The initial search yielded 85 articles that met the inclusion criteria and contained one or more keywords describing AD, diet, cognition, high glycemic index, KD, and MCT supplementation. The abstracts of these studies were screened and judged if the content answered the PICOT question. Cited articles were also screened for inclusion criteria, and their abstracts were scanned for content answering the PICOT question. The author identified fifteen articles for this review based on attributes aligning with inclusion criteria. During this process, recurring themes emerged and are represented in the following categories for synthesis and reporting.

Impact of High Glycemic Index (GI) Diets and Insulin Resistance

Current research explores the effects of glucose and high glycemic diets on cognition; other research is focused on type 2 diabetes, hyperglycemic states, and their impact or correlations with cognitive impairment and AD.

Gentreau et al. (2020) investigated the associations between high glycemic index diets and cognitive decline. This longitudinal study compared APOE4- genes associated with amyloid deposition of AD- carriers with noncarriers and found that high glycemic load foods were significantly associated with cognitive decline in visual memory, episodic memory, and

global cognition compared to low glycemic index foods (Gentreau et al., 2020). When compared to APOE4 carriers without cognitive impairment, cognitively impaired APOE4 carrier patients scored better on executive function tests after they switched from high GI diets to low GI diets. Furthermore, researchers found that breakfast and afternoon snacks with high GI were associated with cognitive decline and can contribute to the development of dementia (Gentreau et al., 2020).

Thomassen et al. (2020) performed a nationwide prospective cohort study of 784,434 Danes above the age of 65, focusing on individuals with type 2 diabetes. They used the Mendelian randomization strategy and found that type 2 diabetes is significantly correlated with the development of dementia, with a hazard ratio of 1.13 (1.06-1.21) for AD (Thomassen et al., 2020).

Zhou et al. (2023) performed a meta-analysis of 47 studies, including 2,981 patients. The authors compared the fasting blood glucose (FBG) of patients with AD and control groups and found that the AD patient group had higher FBG with statistical significance ($p < .001$, 95% C.I.s (0.65, 1.23)). They found that in patients with elevated blood glucose levels caused by impaired glucose metabolism, reduced sensitivity of insulin receptors, and brain insulin resistance showed significant declines in learning, memory processing, and cognitive function. These patients were at increased risk for developing or worsening cognitive impairment related to AD (Zhou et al., 2023). The researchers also found that improving brain glucose metabolism can potentially treat cognitive impairment in AD (Zhou et al., 2023).

Mullins et al. (2018) measured brain glucose and other metabolites in 79 subjects: 27 young controls, 27 elderly controls, and 25 with AD using Magnetic Resonance Spectroscopy

and compared these results with young, metabolically fit subjects. They found significantly elevated glucose levels in several brain areas of the patients with AD compared to older or younger control groups, elevation due to impaired glucose uptake and metabolism, also seen in type 2 diabetes. The authors, therefore, concluded that in patients with AD, brain insulin resistance causes impaired glucose metabolism and metabolites of glucose oxidation, which have toxic effects and have been associated with memory deficit (Mullins et al., 2018).

Taylor et al. (2017) conducted a longitudinal study of 128 cognitively intact sedentary individuals aged 65 and 90 lasting for 52 weeks. The researchers assessed the participants' diets using the Diet History Questionnaire (DHQ) II (20), a semiquantitative food-frequency questionnaire with 134 food items, and the daily intake of carbohydrates was calculated. Participants underwent PET scans to assess for amyloid burden in specific brain areas for six regions of interest: anterior cingulate, posterior cingulate, precuneus, inferior medial frontal, lateral temporal, and superior parietal cortex. Researchers found that subjects who consumed a high glycemic load diet (HGLD) had higher amyloid burden in these areas ($P \leq 0.05$), even though they did not display cognitive deficits. Compared to subjects who consumed a diet with decreased carbohydrate content, scans showed a non-elevated amyloid burden. When the cognitive assessment scores of these two groups were compared, subjects with HGLD showed poorer cognitive performance when using the MMSE, Wechsler Adult Intelligence Scale-Revised, fluency, or block design. While this study population did not include individuals with AD, the findings are relevant to the pathophysiology of AD.

Impact of Diets with High Lipid Content

The brain requires 20% of the body’s total energy expenditure at rest to support

synaptic transmission, maintain ion gradients, neuronal signaling, phospholipid synthesis, cytoskeleton remodel and repair, and axonal transport. When the glucose supply is restricted or inadequate, the brain uses alternate fuel sources, such as KB, acetoacetate, and MCT, as long as their concentration in the bloodstream is adequate (Cunnane et al., 2020).

Jensen et al. (2020) summarized current knowledge of KD and its cognitive benefits, where KD improved blood flow in several brain regions in patients with mild to moderate AD. The authors described a small study where diet-induced hyperketonemia has produced improvements in verbal memory in subjects with mild to moderate AD. After six weeks of KD, patients with mild to moderate cognitive decline experienced improved verbal memory performance (Jensen et al., 2020). Similarly, in three studies, researchers observed improvement of cognitive impairment in patients with mild to moderate AD. Exogenous ketone administration improved memory retrieval, mood, and performance of ADLs, as described in a single case study in the review (Jensen et al., 2020).

In a double-blinded randomized control trial study, Henderson et al. (2020) studied 413 participants with mild to moderate AD, where half the participants consumed 10-40 mg of caprylic triglyceride mix daily, and the other half consumed a regular diet. The participants underwent cognitive testing after 26 weeks and lab tests assessing for beta-hydroxybutyrate (BHB), a ketone metabolite in the blood of participants from both groups. The researchers found similar pre-treatment and placebo BHB levels, which improved post-treatment. The researchers concluded against the cognitive improvement, which was evident but statistically insignificant ($p = .2458$), noting that dietary intake of KB assessed in the participants' blood as ketones were only modestly elevated and thus could not improve cognition and reasoning. The

authors concluded that the participants did not reach sufficient levels of ketosis necessary for the brain to convert glucose into BHB usage, which appears to be an important aspect of KB supplementation to achieve cognitive improvement (Henderson et al., 2020).

In a quasi-experimental design study by Ota et al. (2019), the researchers studied 20 patients with mild to moderate AD who were given a ketogenic mix of MCT daily consumed at different rates and doses. The researchers observed statistically significant improvement ($P < .05$) in many cognitive areas, such as block design, digit symbol coding, and immediate and delayed logical memory, with a maximal level of improvement eight weeks into the trial. (Ota et al., 2019). In this sample of 20 patients, KD improved cognitive functions, learning, and spatial memory. Supplementation with MCTs contributed to an improvement of the working memory and cognitive functions in patients with AD as well as in individuals without dementia: improvement in cognitive function by 2.12 ± 8.70 points on the ACE-III scale, an improvement in everyday functioning by 3.12 ± 5.01 points on ADCS-ADL scale and an improvement in the quality of life by 3.37 ± 6.86 points on the Quality of Life in AD (Ota et al., 2019).

In a randomized controlled trial, Xu et al. (2019) compared MCT and placebo effects on cognition, reasoning, praxis, and ADLs of 53 patients with mild to moderate AD. They found no significant changes between groups; however, when accounting for the APOE4 gene alleles, the MCT supplementation group showed statistically significant improvement in cognition and had improved ADAS-Cog-C and ADL scores ($p < .01$) (Xu et al., 2019).

Tao et al. (2022) performed a systematic review of pertinent RTC and crossover studies and found nine articles studying the effects of KD and MCT on the cognition of 386 patients with AD. Of the nine studies, six concluded that KD or MCT supplementation significantly

improved ADAS-cog scores. The researchers found that administering a KD improved cognition, episodic memory, language, executive function, and processing speed (Tao et al., 2022).

Phillips et al. (2021) recruited 26 patients with a diagnosis of mild to moderate AD. For 12 weeks, half of the participants were given a KD using low-cost ingredient recipes and dietary recommendations aligning with the KD when eating out. This period was followed by a ten-week washout when the participants returned to their previous diet. After this, the participants consumed a regular, low-fat, healthy diet for 12 weeks. The control group started the regular low-fat diet for 12 weeks, then ten weeks of washout period when they consumed their usual diet, after which they started 12 weeks of the KD. The researchers did not use MCT due to increased gastrointestinal side effects and possible noncompliance or dropout rates due to side effects. Initial ADL and cognitive assessments were administered; the researchers calculated dementia severity scales at a mean of 12.1 and repeated the evaluation at weeks 6 and 12. Data gathered shows significant improvements in cognition: ACE-III of + 2.12 ± 8.70 points, P = .24, ADL scores by week 6, + 3.13 ± 5.01 points, P = .0067, and quality of life QOL-AD of + 3.37 ± 6.86 points, P = .023, with a slight decline by week 12 (which might have been influenced by Covid-19 isolation during the time of the experiment). The quality of life scores also showed considerable improvement (Phillips and al., 2021).

In a small pilot study, Taylor et al. (2022) compared the effects of MTC-containing KD in 15 participants with mild to moderate AD. In the ten patients who completed the pilot study, the researchers noted significant improvements of 4.1 points in ADAS-Cog scores (P = .02) while consuming a KD, which reverted to previous levels during the washout period (Taylor et al.,

2022).

Lilamand et al. (2020) reviewed 11 animal and 11 human studies in a translational review. The researchers pointed out many flaws in the included studies, such as inconsistent study designs, assessment procedures, and interventions neglecting genetic mutations that contribute to the development of AD, such as the expression of APOE4 and type 2 diabetes. After analyzing the study results, where six out of ten human studies showed significant cognitive improvement in human subjects in the intervention groups, the authors concluded that KD might be a promising way to improve outcomes of cognitive impairments in AD. They also noted that many RTCs showed more significant cognitive score improvements in patients with the non-APOE4 phenotype (Lilamand et al., 2020).

Fortier et al. (2020) conducted an RCT study with 83 participants: 39 using a 30g/day daily intake of ketogenic MCT and 43 using a regular diet. The participants had similar male-to-female ratios, cognitive scores, and APOE4 allele backgrounds; they were assessed using MoCA and MMSE scores at baseline and six months. After six months, they concluded that the change in plasma total ketones correlated positively with the change in several cognitive tests of episodic memory, executive function, and language, with coefficients of correlation of $r = +.229$ to $+0.325$ ($P < .042$ to $.0028$) (Fortier et al., 2020).

Xu et al. (2023) conducted a systematic review of the current literature regarding KD and its effect on patients with AD. The included 29 human studies, ranging from 6 to 208 participants with mild to moderate AD, and a total of 1024 participants using the KD or 30 to 42 grams per day MCT supplements, ranging from 2 weeks to 90 days. Twenty studies found improved

patients' cognition, ADL performance, and executive memory functions. This change is attributed to many mechanisms: improved white matter energy supply, brain functional connectivity, and axonal integrity. KD decreases brain inflammation, a characteristic of AD, which is neurotoxic and can lead to neuronal loss and cognitive dysfunction. (Xu et al., 2023).

Lilamand et al. (2021) systematically reviewed four animal models and eight human studies. All animal studies with genetically modified mice mimic AD behavior and physiologic changes. The mice showed cognitive improvement and decreased amyloid formation when fed a KD or BHB supplement. The eight human studies included 384 patients; many were crossover trials, where participants took KD supplements and then changed to a regular diet at midpoint. These studies lasted between two and 26 weeks. Five out of eight showed positive cognitive changes, such as memory improvement and executive functioning; also, three out of the eight studies assessed and showed positive changes in blood BHB/ ketone levels during supplementation. The length of the intervention as well as the amount of KD or BHB supplements and increased plasma BHB concentrations, were positive predictors for cognitive and executive function improvement in subjects with AD and mild to moderate cognitive impairment (Lilamand et al., 2021).

Bai et al. (2023) researched the effects of the KD in patients with type 2 diabetes (T2DM). In this systematic review, when compared to patients without diabetes, patients with type 2 diabetes have a higher incidence of AD, a relative risk of 1.21 for mild cognitive impairment, and a 50 to 100% chance of developing dementia, including AD. The researchers also found that KD has been shown to have neuroprotective effects by decreasing amyloid burden and amyloid toxicity, lowering oxidative stress, regulating energy metabolism, and

controlling inflammation, all of which have been linked to cognitive impairment. They also conclude that the disruption of the blood-brain barrier (BBB), which can occur in AD, is linked to cognitive impairment. KD has been shown to restore the BBB, and thus improve cognition (Bai et al., 2023).

Synthesis of the Literature

AD is a slow-progressing illness; amyloid plaque can accumulate over a period of 10 to 15 years before the onset of clinical memory impairment (Taylor et al., 2017). PET scan studies show that many patients have an increased amyloid burden and detectable tau protein tangles; however, they do not (yet) show signs of cognitive impairment. These patients are at a higher risk for developing cognitive decline and brain atrophy than those patients without amyloid burden (Taylor et al., 2017). When the patient begins to show signs of cognitive impairment, the brain matter changes, and white matter loss is too advanced, the deposition of amyloid plaques and tau protein tangles is irreversible, and patients experience cognitive impairment, which conventional AD medications may slow, but cannot reverse.

The literature review concurs with the WHO's guidelines regarding AD development risk reduction, which states that diet is an important modifiable risk factor in AD development (World Health Organization, 2019). A diet high in carbohydrates is linked to hyperglycemia, impaired glucose metabolism, insulin resistance, and type 2 diabetes. Impaired glucose metabolism in the brain and high carbohydrate intakes were inversely correlated with cognitive performance. Patients who used regular Western or other high glycemic index diets had similar and significantly advanced cognitive impairment when compared to patients who consumed a Mediterranean low carbohydrate diet they also scored significantly lower on cognitive

assessment tests and had lower global cognitive performance (Taylor et al., 2017).

Many research articles suggest that T2DM has many similarities to AD, considered insulin resistance of the brain. The brains of patients with AD contain high levels of glucose and byproducts of glucose metabolism, and they are unable to use this energy substrate to produce energy. These byproducts are toxic to neural tissue and lead to neuroinflammation and neural cell death, causing cognitive impairment or worsening cognitive decline.

In the presence of impaired glucose metabolism, the brain can use KB, lipids, and MCT supplements to produce energy. Intake of these healthy lipids measured in the blood of patients with mild to moderate AD has been shown to produce improvement in ADLs, critical thinking, problem-solving, and short-term memory; thus, mild to moderate cognitive decline of AD can be improved (Xu et al., 2019). Besides KB, consuming a high protein, high fat, and low glycemic index diets such as low carb or KD, the consumed healthy fats can be used by the brain for energy production. This diet also decreases neuroinflammation, stops neuronal cell death caused by ROS or other neurotoxic metabolites, decreases amyloid burden and tau deposits, and improves the BBB, which has been shown to improve cognition in patients with mild to moderate AD (Bai et al., 2023).

Implications for Family Nurse Practitioners

Family nurse practitioners (FNP) provide primary, secondary, and tertiary prevention services to a large variety of populations, from healthy adults to older adults with mild to moderate cognitive impairment (Dunphy, 2023). FNPs are the first providers who encounter patients and their family members with concerns about memory impairment, decline in critical thinking, and decreased ability to perform previous activities. FNPs should be aware of AD

pathology and the fact that AD develops over decades (Taylor et al., 2017). This knowledge allows ample time to educate 30- 40-year-old patients regarding their diet and the deleterious effects of high dietary intake of simple carbohydrates on their blood glucose levels, the development of type 2 diabetes, as well as insulin resistance in the brain, worsening amyloid burden and tau protein tangles, which can lead to the development of AD and cognitive impairment (Taylor et al., 2017).

FNPs should educate their patients regarding reduction in simple carbohydrate intake, especially high glycemic index food items, refined and simple sugars, which cause neuroinflammation, increased amyloid burden, and tau protein hyperphosphorylation, leading to the development of AD. Increasing intake of healthy fats in the form of KB, BHB, or MCT supplementation has a beneficial effect on healthy individuals and patients with AD with mild to moderate cognitive impairment. Besides these dietary changes, patients interested in carbohydrate reduction can consume low-carb or KD, which are delicious, easy to prepare, and provide healthy fats ideal for optimal brain functioning. Many KB supplements are readily available on the market, and further supplementation with foods high in these fats, such as coconut oil, palm kernel oil, and goat milk, can also have similarly beneficial effects (Phillips et al., 2020). Furthermore, FNPs should encourage the consumption of healthy fats, such as fish-derived polyunsaturated fatty acids, fish, nuts, and olive oil, which is also recommended by the WHO along with fruits and vegetables, as part of the Mediterranean-like diet, to reduce cognitive impairment and risk for dementia (World Health Organization, 2019).

Implications for Health Policy and Future Research

FNPs have the skills and knowledge needed to have a meaningful impact on the health of

communities and can make policy changes to improve the lives of their patients and the population as a whole. FNPs can sit on committees, and state nursing organizations, advise and educate the public, and help create or review health legislation (Koloff, 2020). FNPs should contribute to changing health policy by passing new legislation or adjusting existing law by employing Longest's framework for policy making: the acronym CHANGE (Eden et al., 2020). Collecting (C) research data from RCT, reviews, and meta-analyses reporting that cognitive impairment is closely related to neuroinflammation, high glycemic index diet, chronic hyperglycemia, and brain insulin resistance, causing amyloid plaque deposition, tau protein tangles, and neuronal death. The best approach (H) to solving the problem is to consume low glycemic index foods and adequate MCT supplementation, which improves cognition and reduces neuroinflammation in mild to moderate AD. Meeting with associations (A) and stakeholders, such as the Society of Metabolic Health Practitioners, who published clinical guidelines supporting dietary carbohydrate reduction and its benefits as a therapeutic intervention (Hite, 2022). Support from other disciplines and input from key stakeholders will likely help execute and pass legislation. The next step is finding a sponsor who negotiates (N) the bill through the legislature. Gathering (G) support from the public via social media, sending informational emails to organizations, and employing public voices can have a significant impact on the dissemination of research data. These outlets draw public attention to the neuro-inflammatory effects of high glycemic index diets, as well as the beneficial effects of KD and MCT supplements on cognition, neuroinflammation, and cognitive improvement in multiple areas of critical thinking, problem-solving, and self-care and the way these diets can impact patients with mild to moderate AD as well as their caretakers and families. FNPs should continue

as experts (E) in the field and be thoroughly knowledgeable of the pros and cons of the bill, i.e., why or why not dietary modifications in the form of reduced carbohydrate intake would be beneficial to improve cognition in AD (Eden et al., 2020).

Dietary changes in the form of low carbohydrate, KD, or MCT supplementation show promising results when used adequately, consistently, and for extended periods. These diets have been shown to have minimal side effects and do not affect the cardiovascular system. However, they show promising results in cognition improvement and critical thinking in patients with mild to moderate AD Large R.C.T.s, meta-analyses, and systematic reviews are needed to explore these diets' long-term positive and possible adverse effects on cognition and neuroinflammation.

Summary and Conclusion

AD affects every eighth person in the U.S. and is the 10th leading cause of death worldwide. It usually affects the older adult population, and it is characterized by impaired cognitive function, memory, abstract thinking, and problem-solving. AD develops over decades, and its hallmark features are amyloid-beta deposits, tau protein tangles, and reduction in the white brain matter. Chronic hyperglycemia and insulin resistance in the brain contribute to ineffective amyloid processing and hyperphosphorylation of tau proteins. Impaired neuronal energy production and cell instability lead to neurodegeneration and cognitive impairment. Diets high in carbohydrates contribute to neuroinflammation and impaired blood flow in the brain; people who consume high glycemic index diets have inferior cognitive scores when compared to those who consume a low carbohydrate diet (Phillips et al., 2020). KD, KB, BHB, and MCT supplementation showed beneficial effects in improving cognition in healthy and older adults

with AD and mild to moderate cognitive impairment (Taylor et al., 2017). FNPs should educate their patients regarding these findings and encourage them to decrease their carbohydrate intake and increase their healthy fat intake or supplement their diet with KB, BHB, or MCT to improve and preserve their cognitive ability.

FNPs provide care for patients with AD who have cognitive impairment frequently; these patients and their caregivers should be counseled regarding dietary changes and KB or MCT supplementation, as well as routine medical management. Consuming a diet low in simple carbohydrates and high in fatty acids, such as KD, or using KB, MCT, or fatty acid supplements was shown to have positive effects on decreasing neuronal inflammation; they provide a healthy energy substrate, which restores mitochondrial function and decreases inflammatory marker presence in the brain. Patients with mild to moderate AD who consumed a diet rich in fatty acids, KB, or a KD had improved scores on cognitive assessment scales, an effect which declined when switched back to a high carbohydrate diet.

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