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Featured Article

Feasibility and efficacy data from a ketogenic diet intervention in Alzheimer's disease

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Abstract

Introduction: We assessed the feasibility and cognitive effects of a ketogenic diet (KD) in participants with Alzheimer's disease.

Methods: The Ketogenic Diet Retention and Feasibility Trial featured a 3-month, medium-chain triglyceride–supplemented KD followed by a 1-month washout in clinical dementia rating (CDR) 0.5, 1, and 2 participants. We obtained urine acetoacetate, serum β-hydroxybutyrate, food record, and safety data. We administered the Alzheimer's Disease Assessment Scale-cognitive subscale and Mini–Mental State Examination before the KD, and following the intervention and washout.

Results: We enrolled seven CDR 0.5, four CDR 1, and four CDR 2 participants. One CDR 0.5 and all CDR 2 participants withdrew citing caregiver burden. The 10 completers achieved ketosis. Most adverse events were of medium-chain triglyceride–related. Among the completers, the mean of the Alzheimer's Disease Assessment Scale-cognitive subscale score improved by 4.1 points during the diet ($P = .02$) and reverted to baseline after the washout.

Conclusion: This pilot trial justifies KD studies in mild Alzheimer's disease.

Keywords: Alzheimer's disease; Cognition; Ketogenic diet; Low-carbohydrate diet; Medium-chain triglyceride

1. Introduction

Aberrant energy metabolism occurs in Alzheimer's disease (AD) animal models and patients [1]. It manifests as perturbed mitochondrial function and structure as well as during fluorodeoxyglucose positron emission tomography evaluations. Fluorodeoxyglucose positron emission tomography reveals focal reductions in brain glucose utilization with advancing age [2,3], which extend in magnitude and distribution during AD [4,5]. Neuron loss, synaptic degradation, or bona fide bioenergetic changes could contribute to this, although changes in asymptomatic subjects with AD risk factors suggest that bona fide changes exist [6–8]. Brain homogenates of AD subjects also show less glucose consumption than control homogenates [9], even though homogenization disrupts synapses and neutralizes their impact; persistence of reduced glucose flux in homogenates suggests that diminished synaptic connectivity does not exclusively account for reduced AD glucose utilization.

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In AD, targeting bioenergetic defects and decreased glucose utilization for therapeutic purposes is reasonable [10]. One potential approach includes the ketogenic diet (KD). KDs increase fat and reduce carbohydrate consumption [11]. This reduces insulin, which stimulates liver oxidation of fatty acids to ketone bodies (β-hydroxybutyrate [BHB], acetoacetate, and acetone) that enter the blood. BHB and acetoacetate access the brain and fuel respiration [12]. Acetone also circulates, it may access the brain, and ventilation facilitates its excretion. Given a choice between ketone bodies and glucose, neurons preferentially consume ketone bodies [13–15]. Although brain glucose utilization declines in AD, ketone body utilization does not [16].

Here, we considered the previously proposed question [17] of whether a KD can benefit cognition in AD. Although studies report that ketosis-like diets improve memory in cognitively intact or mild cognitive impairment participants [18–20] and that a simple medium chain triglyceride (MCT)-induced ketosis may improve AD cognition [21,22], whether a true KD affects cognition in actual AD patients or is even feasible remains unclear. Adding to the relevance of this question, KDs differ from MCT-limited approaches in terms of ketone body pharmacokinetics, dietary fat intake, insulin signaling effects, and inflammation effects. We therefore tested the feasibility of maintaining AD participants on a KD and acquired preliminary insight into how a KD affects cognition in AD participants.

2. Methods

2.1. Overall study design and recruitment

The Ketogenic Diet Retention and Feasibility Trial (KDRAFT) was a single-arm, pilot clinical study with a target enrollment of 15 participants with AD. The protocol required participants to maintain an MCT-supplemented KD for 3 months and immediately on completing this intervention to discontinue that diet and resume a normal diet for 1 month (thereby defining a 1-month washout period). Because from a calorie intake perspective, our diet increased dietary fat consumption and added MCT to offset lowered carbohydrate consumption, to distinguish our diet from a low-carbohydrate, calorie-restricted KD; we herein refer to our diet intervention as a very high-fat KD (VHF-KD).

To recruit for this trial, we first identified potential participants from a registry database maintained by the University of Kansas Alzheimer's Disease Center. Then, we informed potential participants about the study opportunity through one of two approaches. One approach used letters or phone calls to initiate discussion of this opportunity. Alternatively, we invited potential participants to a KD cooking demonstration at the University of Kansas (KU) Clinical Research Center Demonstration Kitchen and used this event to initiate discussion of the research opportunity.

2.2. Participants

The participants met McKhann et al. criteria for AD [23]. Individuals were eligible to participate in the study if they had a clinical dementia rating (CDR) of very mild AD (CDR 0.5), mild AD (CDR 1), or moderate AD (CDR 2). No clinically significant electrolyte, renal, or liver function abnormalities, a body mass index (BMI) $\geq$ 21 kg/m^2, English mastery, and an active study partner were also required. Exclusion criteria included serious medical risks including type 1 diabetes, ongoing or recent cancer, a cardiac event in the past year, or other conditions deemed serious risks by physicians on the study team. The KU Medical Center's Institutional Review Board approved the protocol. Informed consent was obtained from all study participants as per institutional guidelines.

2.3. The VHF-KD intervention and dietary intake evaluations

Participants received nutrition counseling from the study dietitian at the baseline study visit. Targeted macronutrient composition for the dietary intervention included approximately 70% of energy as fat (including the MCT), 20% of energy as protein, and restriction of carbohydrate to less than 10% of energy; we sought a ketogenic ratio of 1:1 (ratio of lipid consumption in grams to nonlipid consumption in grams) or better. Energy intake requirement and targeted daily MCT dosage was estimated using the Mifflin-St. Jeor equation [24]. A monthly supply of MCT oil (Now Foods, USA), which contained a combination of C8:0 and C10:0 fatty acids, was provided at each study visit. In general, the MCT dosage provided approximately 10% of total energy from fat during the first week and increased by increments of 10% during each successive week until reaching 40%, while allowing for titration adjustments based on participant tolerance. Participants could choose to consume the MCT neat or mix it with food or beverages. We provided daily multivitamin, vitamin D, calcium, and phosphorus supplements to help prevent micronutrient deficiencies. On completion of the VHF-KD, participants were instructed to return to a normal diet to complete a 1-month washout period.

2.4. Objectives and outcomes

Our primary objective was to address the feasibility of implementing a VHF-KD intervention in AD participants. Secondary objectives included evaluating the effects of a VHF-KD on cognition.

2.4.1. Dietary assessment

At the baseline visit, the study dietitian provided instructions to the participant's study partner for completing 3-day food records (3DFRs). Each 3DFR recorded intake for two weekdays and one weekend day. We entered 3DFR data into the Nutrition Data System for Research (version 2016) to analyze nutrient intake. We collected 3DFRs