REVIEW

To Keto or Not to Keto? A Systematic Review of Randomized Controlled Trials Assessing the Effects of Ketogenic Therapy on Alzheimer Disease

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ABSTRACT

Alzheimer disease (AD) is a global health concern with the majority of pharmacotherapy choices consisting of symptomatic treatment. Recently, ketogenic therapies have been tested in randomized controlled trials (RCTs), focusing on delaying disease progression and ameliorating cognitive function. The present systematic review aimed to aggregate the results of trials examining the effects of ketogenic therapy on patients with AD/mild cognitive impairment (MCI). A systematic search was conducted on PubMed, CENTRAL, clinicaltrials.gov, and gray literature for RCTs performed on adults, published in English until 1 April, 2019, assessing the effects of ketogenic therapy on MCI and/or AD compared against placebo, usual diet, or meals lacking ketogenic agents. Two researchers independently extracted data and assessed risk of bias with the Cochrane tool. A total of 10 RCTs were identified, fulfilling the inclusion criteria. Interventions were heterogeneous, acute or long term (45–180 d), including adherence to a ketogenic diet, intake of ready-to-consume drinks, medium-chain triglyceride (MCT) powder for drinks preparation, yoghurt enriched with MCTs, MCT capsules, and ketogenic formulas/meals. The use of ketoneurotherapeutics proved effective in improving general cognition using the Alzheimer's Disease Assessment Scale-Cognitive, in interventions of either duration. In addition, long-term ketogenic therapy improved episodic and secondary memory. Psychological health, executive ability, and attention were not improved. Increases in blood ketone concentrations were unanimous and correlated to the neurocognitive battery based on various tests. Cerebral ketone uptake and utilization were improved, as indicated by the global brain cerebral metabolic rate for ketones and [^{11}C] acetoacetate. Ketone concentrations and cognitive performance differed between *APOE* ε4(+) and *APOE* ε4(−) participants, indicating a delayed response among the former and an improved response among the latter. Although research on the subject is still in the early stages and highly heterogeneous in terms of study design, interventions, and outcome measures, ketogenic therapy appears promising in improving both acute and long-term cognition among patients with AD/MCI. This systematic review was registered at www.crd.york.ac.uk/prospero as CRD42019128311. *Adv Nutr* 2020;11:1583–1602.

Keywords: ketosis, MCT, neurologic disease, dementia, cognitive impairment, ketoneurotherapeutics, cognitive decline, brain metabolism, amyloid, APOE

Introduction

Alzheimer disease (AD) is the most prevalent form of progressive dementia (1), and is expected to increase in prevalence as a result of the aging boom generation (2). As a result, AD is considered a "growing global health concern" (3), with ∼70% of the cases being attributed to a genetic predisposition, and the remaining effectors stemming from the environment (3). AD is characterized by brain accumulation of pathological amyloid β (Aβ), predating the initiation of cognitive impairment by ∼1 decade (4–6).

On the primary prevention level, diet has been shown to either accelerate, or delay AD onset, with many cohort studies supporting the existence of this relationship (7). Fish intake (8–10) and greater adherence to traditional dietary patterns rich in antioxidants, PUFAs, and MUFAs like the Japanese, Argentinean, and Mediterranean diets (11) have been shown to postpone AD onset. In parallel, other healthy diet regimes, like the Dietary Approaches to Stop Hypertension (DASH), and the Mediterranean-DASH Intervention for Neurodegenerative Delay diets (12–14),

have also been shown to protect against the development of AD. A recent meta-analysis revealed that adherence to an AD protective dietary pattern induced a significantly lower deposition of Aβ, although this difference was not clinically important (15).

During AD, a progressive synaptic dysfunction is taking place, resulting in neuronal death (16, 17), developing a deficit in brain glucose utilization as a result of the reduced neuron count (18). In parallel, nutrient deprivation reduces mitochondrial ATP synthesis. In turn, the observed mitochondrial dysfunction compromises brain regulation of the glucose transporter GLUT1, further aggravating brain glucose uptake and glycolysis (19, 20). The loss of neurons and the impaired brain substrate use exert a synergistic effect in tamping down cognitive function. Adherence to a high-glycemic diet is associated with an increased cerebral amyloid burden among older adults (21). To correct the induced substrate deficit, the use of ketogenic therapy has been proposed and assessed in both animal (22–24) and human studies (25–32). Popular ketogenic remedies include *1*) the adherence to ketogenic diet (KD) (high fat content at the expense of carbohydrates) and *2*) the intake of medium-chain triglycerides (MCTs) with 6–12 carbon atoms, which are metabolized in the liver (33–35). Owing to the surplus of fatty acid availability, their breakdown synthetizes ketones, which in turn produce acetyl-CoA (36). Accumulating experimental data suggest that ketoneurotherapeutics entail neuroprotective benefits for the ageing brain (35, 37, 38), by replicating the effects of caloric restriction, boosting the production of ketone bodies (39–41), and increasing energy availability.

The aim of the present study was to systematically review all randomized controlled trials (RCTs) assessing the efficacy of ketogenic therapy among patients with AD or mild cognitive impairment (MCI).

Methods

Study design and protocol

The present systematic review was based on a predefined protocol registered in PROSPERO (CRD42019128311), and adhered to the reporting guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (42).

Research question and search strategy

A systematic search was conducted on PubMed, CochranE coNTrolled Register of triALs (CENTRAL), ClinicalTrials.gov, and gray literature, for trials published in the English language assessing the effect of ketogenic therapy on AD indicators, published until 1 April, 2019.

The research question was addressed in the form of population, intervention, control, and outcomes (PICO) as follows: in patients with an MCI and/or AD diagnosis (P), what is the efficacy of ketogenic therapy via adherence to a KD, or consumption of ketogenic agents/supplements/meals (I), compared with placebo/usual diet or non–ketogenic agent administration (C) on disease-related indicators such as cognition or biomarkers associated with AD (O)?

Keywords used in the searches included (ketogenic), (ketosis), (ketone), (MCT), (medium-chain triglycerides), (beta-hydroxybutyrate), (caprylic), (acetoacetate), (Alzheimer), (Alzheimer's disease), and (mild cognitive impairment). **Supplemental Figure 1** presents the detailed search string for PubMed.

Eligibility criteria

Two reviewers independently performed the search and selected eligible trials. In the case of disagreement concerning the eligibility of a study, a third reviewer weighed the evidence to provide a solution.

Inclusion criteria involved all *1*) clinical trials; *2*) performed on adult humans; *3*) assessing the effect of nutritional ketosis on AD indicators; *4*) compared against placebo, usual diet, or meals lacking ketogenic agents; and, *5*) published in the English language. No restrictions were applied concerning the duration of the studies, ketogenic therapy mode (diet/supplementation), ketone dose, cognitive outcomes, participant's sex, age, or sample size.

Reasons for trial exclusion involved *1*) clinical trials without a comparator group; *2*) results published in languages other than English; *3*) involving nutritional or pharmacological interventions not inducing nutritional ketosis; *4*) trials performed on animals; *5*) including healthy participants or patients without cognitive impairment, AD, or dementia; *6*) trials performed on children (<18 y old); or, *7*) examining the effects of diabetic ketoacidosis.

Data extraction

Data were extracted by 2 independent reviewers in standardized forms. In cases of disagreement, a third reviewer resolved the issue. Extracted data included study details (first author, year of publication, masking of interventions, multicenter design and countries involved, design, having informed consent/approval of protocol, source of funding, duration), AD diagnostic criteria, detailed intervention and

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Supplemental Figure 1 is available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances.
Address correspondence to MGG (e-mail: mariagram@auth.gr).
Abbreviations used: AcAc, acetoacetate; AD, Alzheimer disease; ADAD-Cog, Alzheimer's Disease Assessment Scale-Cognitive; *APOE* ε4, apoε4 allele; Aβ, amyloid β; BEAM, Brain Energy and Memory; BENEFIC, Brain ENErgy Fitness, Imaging and Cognition; BHB, β-hydroxybutyrate; BNT, Boston Naming Test; BVMT-R, Brief Visuospatial Memory Test-Revised; CMR, cerebral metabolic rate; CSF, cerebrospinal fluid; DASH, Dietary Approaches to Stop Hypertension; *IDE*, insulin-degrading enzyme; *IL1B*, interleukin 1β; KD, ketogenic diet; MCI, mild cognitive impairment; MCT, medium-chain triglyceride; MMSE, Mini-Mental State Exam; MoCA, Montreal Cognitive Assessment; MUFA, mono-unsaturated fatty acids; PET, positron emission tomography; PUFA, poly-unsaturated fatty acids; rCBF, regional cerebral blood flow; RCT, randomized controlled trial; RL/RI-16, Rappel Libre/Rappel Indicé; RoB, risk of bias; SNP, single nucleotide polymorphism; spm, statistical parametric mapping; sVOI, standardized volumes of interest; TMT, Trail Making Test; t-tau, total tau; VF, verbal fluency; V-PAL, Verbal Paired Associate Learning Test; WMS-R, Wechsler Memory Scale-Revised.

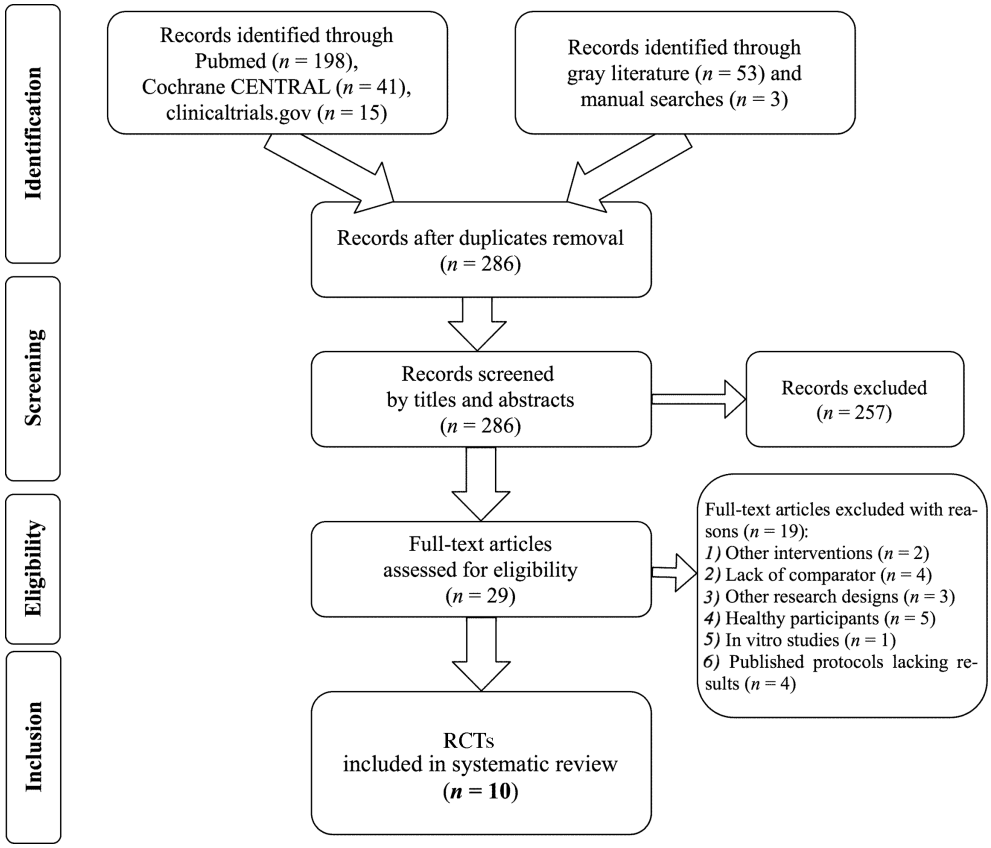

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (42) flowchart of the study selection process for the identification of RCTs investigating the effects of ketogenic therapy on patients with Alzheimer disease or mild cognitive impairment. RCT, randomized controlled trial.

comparator group characteristics (age, *n*, female ratio, condition, etc.), intervention and comparator characteristics (duration of intervention and washout), compliance assessment, primary and secondary outcomes, results, and other trial characteristics (funding, country of implementation, trial registry and number, dropouts, adverse events, evaluation time points, etc.).

Risk of bias

Eligible studies were assessed for bias with the Cochrane Risk of Bias (RoB) tool (43). Two authors examined the studies for sources of bias and concluded if there were low, high, or moderate concerns of bias regarding the randomization process, deviations from the intended interventions, measurement of the outcomes, missing outcome data, selection of the reported results, and overall bias. Disagreements were resolved by discussion with a more experienced investigator.

Quality assessment of the studies

The Oxford quality score (44) was applied to each RCT by 2 independent reviewers. This score assesses and assigns a positive value of 1 based on the randomization criteria, masking, and adequacy in the reporting of withdrawals and dropouts. In addition, 1 point is deducted when the randomization scheme or the masking is not deemed appropriate.

Results

Search results and characteristics of the retrieved trials

Out of 310 entries in total, 10 RCTs (45–54) fulfilled the protocol's criteria (**Figure 1**). **Table 1** details characteristics concerning the design and protocol of the included trials. Three RCTs (46, 51, 53) were crossover, and the remainder (48–50, 52, 54) were of parallel design. The majority of trials had a published protocol (45–50, 52), with 2 sharing the same protocol (48, 49). Except for the Ota et al. (51) and Fortier et al. (47) trials that originated from Japan and Canada, respectively, the remaining RCTs were conducted in the United States (45, 46, 48–50, 52–54). By default, masking of diet RCTs was not double-blind, and was either single-blind (45, 46) or open-label (50). **Table 2** stresses the participant characteristics of the included trials. The number of participants in each trial ranged between 6 (52) and 152 (48), all ketogenic treatment–naïve, with MCI or AD diagnosis. Based on the per protocol (PP) analyses, the pooled sample of patients included in the present systematic review involved 456 adults in total.

TABLE 1 Study design and protocol characteristics of the included RCTs investigating the effects of ketogenic therapy on patients with mild cognitive impairment/Alzheimer disease[1]

First author	Brandt (45)	Craft (46)	Fortier (47)	Henderson (48)	Henderson (49)	Krikorian (50)	Ota (51)[2]	Rebello (52)	Reger (53)	Torosyan (54)
Study name	—	BEAM	BENEFIC	—	—	—	—	—	—	—
Study duration	October 2015 to April 2018	February 2015 to April 2017	2015 until now	October 2004 to June 2006	October 2004 to June 2006		NR	October 2012 to August 2013	NR	NR
Publication year	2019	2016	2019	2009	2011	2012	2019	2015	2004	2018
Publication type	Full-text	Abstract	Full-text	Full-text	Full-text	Full-text	Full-text	Commentary	Brief communication	Full-text
Journal	*J Alzheimers Dis*	*Alzheimers Dement*	*Alzheimers Dement*	*Nutr Metab*	*BMC Med Genet*	*Neurobiol Aging*	*Neurosci Lett*	*BBA Clin*	*Neurobiol Aging*	*Exp Gerontol*
Origin	USA	USA	Canada	USA	USA	USA	Japan	USA	USA	USA
Registry	NCT02521818	NCT02984540	NCT02551419	NCT00142805	NCT00142805	NCT00777010	NR	NCT01669200	NR	NR
Funding	*1*) William & Ella Owens Medical Research Fndn *2*) Bright Focus Fndn *3*) NCATS *4*) Hass Avocado Board	*1*) Wake Forest Baptist Medical Center *2*) NIA *3*) Hartman Family Fndn *4*) Dept of Defense *5*) NCATS	*1*) Part-the-Cloud, AA, USA *2*) Mitacs *3*) Université de Sher-brooke	Accera, Inc.	Accera, Inc.	*1*) Robert C & Veronica Atkins Fndn *2*) NIA *3*) Indiana AD Center	*1*) Food Science Institute Fndn, Japan *2*) Meiji Co. Ltd.	NR	NR	*1*) John Douglas French AD Fndn *2*) Accera, Inc.
Ethical permission	Johns Hopkins University, USA	Wake Forest School of Medicine, USA	CIUSSS de l'Estrie–CHUS, Sherbrooke, Quebec, Canada	Essex Institutional Review Board, Lebanon, NJ, USA	Essex Institutional Review Board, Lebanon, NJ, USA	University of Cincinnati, USA	National Center of Neurology & Psychiatry, Japan	Pennington Biomedical Research Center, USA	NR	NR
RCT design	Parallel	Crossover	Parallel	Parallel	Parallel	Parallel	Crossover	Parallel	Crossover	Parallel
Randomization	Random number table	NR	Randomization sequence with 6 consecutive blocks of 10 participants (1:1 ratio)	Permutated block randomization code with a block size of 4 (1:1 ratio)	NR	NR	Randomized sequence NOD	Random number table NOD	NR	By the pharmacy, NOD

(*Continued*)

TABLE 1 (*Continued*)

First author	Brandt (45)	Craft (46)	Fortier (47)	Henderson (48)	Henderson (49)	Krikorian (50)	Ota (51)[2]	Rebello (52)	Reger (53)	Torosyan (54)
Masking	Single-blind	Single-blind (outcomes assessor)	Quadruple-blind	Double-blind	Double-blind	Open label	Double-blind	Double-blind	Double-blind	Double-blind
Multicenter	No	No	No	✓ (23 centers)	✓ (23 centers)	No	No	No	No	No
Concerns	No flowchart, discrepancies between PP analysis and reported dropouts	More outcomes were reported in the protocol registry, lack of flowchart, no tables				Lack of flowchart, most data presented in figures	Patients at each stage were not reported, no flowchart, lack of RCT protocol registry	Very low sample power, lack of statistical analyses and flowchart	Lack of flowchart, data presented in figures	Uneven sample allocation, no flowchart, low sample power in controls
Oxford quality score (44)	2	−1	2	3	3	−1	0	1	0	2

[1]AA, Alzheimer's Association; AD, Alzheimer Disease; BEAM, Brain Energy and Memory; BENEFIC, Brain ENErgy Fitness, Imaging and Cognition; CIUSSS de l'Estrie–CHUS: Centre Intégré Universitaire de Santé et de Services Sociaux de l'Estrie–Centre Hospitalier Universitaire de Sherbrooke; Dept, Department; Fndn, Foundation; NCATS, National Center for Advancing Translational Sciences; NIA, National Institute of Aging; NOD, not other defined; NR, not reported; PP, per protocol; RCT, randomized controlled trial.

[2]The study had a double design: an RCT (presented in the table) and a long-term clinical trial without a comparator (omitted for not fulfilling the inclusion criteria).

RoB and quality of the included RCTs

Figure 2 summarizes the RoB of the included RCTs. In most RoB domains, the included studies demonstrated unclear bias. The Fortier et al. trial (47) exhibited less bias than the rest, whereas the RCT by Krikorian et al. (50) was of unclear bias throughout the RoB categories. Regarding quality, most studies received a low Oxford score, with the 2 trials conducted by Henderson et al. (48, 49) demonstrating the highest quality among all included RCTs.

Concerning the BEAM (Brain Energy and Memory) trial (46), although 1 full-text publication and another abstract were released during the year 2019 after the end of the present systematic search (55, 56), they both included healthy participants in their sample, without restricting recruitment to persons with AD or MCI only.

Intervention characteristics

Table 3 details the intervention characteristics of the included RCTs, their outcomes, and their findings. A great variety of interventions were identified, including adherence to a KD regime (45, 46, 50), ready-to-consume ketogenic drinks (47, 53), MCT powder for the preparation of ketogenic drinks (48, 49), yoghurt enriched with MCTs (52), MCT capsules (54), and a ketogenic meal (51). In parallel, intervention duration varied considerably, ranging from 45 (54) to 180 d (47), whereas 4 RCTs evaluated the acute effects of consuming a ketogenic meal (51–53) or MCT capsules (54). Intervention compliance was evaluated via plasma (46) or urinary ketone concentrations (45, 50), diet records (50, 52), adherence to the Healthy Eating Index (57) for controls, or consumption count (47, 48), or was not reported at all.

Outcomes of interest

As Table 3 displays, a variety of outcomes were assessed in the included trials, involving subjective neurocognitive tests and combinations of tests (batteries), psychological indexes, brain imaging, genetic predisposition, and a variety of biomarkers (blood and biopsy-derived). The Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) (58) and the Mini-Mental State Exam (MMSE) (59) were the most used tests for assessing general cognition. Other cognitive tests applied included the Montreal Cognitive Assessment (MoCA) (60), the Memory Composite Score—comprised of the Hopkins Verbal Learning Test-Revised (61) and the Brief Visuospatial Memory Test-Revised (BVMT-R) (56), the Wechsler Adult Intelligence Scale-3rd (57), and the Wechsler Memory Scale-Revised (WMS-R) (62). Secondary memory was assessed with the Verbal Paired Associate Learning Test (V-PAL) (63), whereas changes in episodic memory were evaluated with the Rappel Libre/Rappel Indicé (RL/RI-16) (64), the BVMT-R (62), or the paragraph recall test. Language ability was assessed with the Boston Naming Test (BNT) (65). For executive ability and attention, the Stroop Color Word Interference (66), Verbal Fluency (VF) (67), Digit Symbol Substitution Test, and Trail Making Test (TMT) (68) were applied.

TABLE 2 Participant characteristics of the included randomized controlled trials assessing the effects of ketogenic therapy on patients with MCI and/or AD[1]

First author	Brandt (45)	Craft (46)	Fortier (47)	Henderson (48)	Henderson (49)	Krikorian (50)	Ota (51)	Rebello (52)	Reger (53)	Torosyan (54)
Patients, *n*	*n* = 14 (CDR ≤ 1, MoCA: 18–25 [2])	*n* = 10 with MCI and prediabetes	*n* = 52 with MCI (69)	*n* = 152 with mild to moderate AD (MMSE: 14–24 [2])	*n* = 131 with mild to moderate AD (MMSE: 14–24 [2])	*n* = 23 with acquired MCI based on the CDR	*n* = 20 AD with MCI (MMSE: 20 ± 4.3 [3])	*n* = 6 AD with MCI (MMSE: 25–28 [2])	*n* = 20 with AD/amnestic MCI	*n* = 16 with mild to moderate AD (MMSE: 10–28 [2])
Women, *n*	*n* = 7	NR	NR	*n* = 85	NR	*n* = 13	*n* = 9	NR	NR	NR
AD diagnostic criteria	NIA-AA	NR	—	NINCDS-ADRDA and DSM-IV	NINCDS-ADRDA and DSM-IV	NR	NINCDS-ADRDA	NIA-AA	NINCDS-ADRDA	NINCDS-ADRDA
Age, y	Intervention[2]: 74 ± 6[3]Control: 69 ± 5[3]	63.6[4]	≥55	51–93[2]	NR	70 ± 6[3]	73 ± 6[3]	58–78[2]	75 ± 7[3]	50–90[2]
Intervention arm, *n*	*n* = 15 (ITT) *n* = 9 (PP)	*n* = 10	*n* = 26 (ITT) *n* = 19 (PP)	*n* = 86 (ITT) (29 recruited later);[5] *n* = 77 (PP)	*n* = 86 (ITT) *n* = 65 (PP)[6]	*n* = 12	*n* = 20	*n* = 2	*n* = 20	*n* = 14
Control arm, *n*	*n* = 12 (ITT) *n* = 5 (PP)	*n* = 10	*n* = 26 (ITT) *n* = 20 (PP)	*n* = 66 (ITT) (11 recruited later);[5] *n* = 63 (PP)	*n* = 66 (ITT) *n* = 55 (PP)[6]	*n* = 11	*n* = 20	*n* = 2	*n* = 20	*n* = 2
Inclusion criteria	✓	✓	✓	✓	✓	✓	NR	✓	✓	✓
Exclusion criteria	✓	✓	✓	✓	✓	✓	NR	✓	NR	NR
Dropouts, *n*	Intervention: 3[7] Control: 6[7] unwilling to change their diet and/or considering participation as difficult	None	Intervention: 6 were therapy intolerant, 2 discontinued for other reasons Control: 2 were therapy intolerant, 3 stopped for other reasons	Intervention: 35 stopped, 3 lost to follow-up, 20 had adverse events, 8 withdrew consent, 2 perceived lack of efficacy, 1 protocol violator, 1 moved, 3 for other reasons. Of these 38, 9 were not analyzed (missing data)	Intervention: 8 had incomplete data Control: 3 had incomplete data	NR	NR	1 GI issues , 1 non-compliant	NR	6 had incomplete data

(*Continued*)

TABLE 2 (*Continued*)

First author	Brandt (45)	Craft (46)	Fortier (47)	Henderson (48)	Henderson (49)	Krikorian (50)	Ota (51)	Rebello (52)	Reger (53)	Torosyan (54)
				Control: 12 stopped, 2 lost to follow-up, 4 adverse events, 5 withdrew consent, 2 lack of efficacy, 1 protocol violator. Of these 14, 3 were not analyzed (missing data)						

[1] AD, Alzheimer disease; CDR, Clinical Dementia Rating (70); DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; GI, gastrointestinal; ITT, intention to treat; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam (59); MoCA, Montreal Cognitive Assessment (60); NIA-AA, National Institute of Aging–Alzheimer's Association (71); NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (72); NR, not reported; PP, per protocol; SD, standard deviation.
[2] Range.
[3] Mean ± SD.
[4] Mean.
[5] More participants were recruited during the study to attain an adequate sample and increase the response rate; however, the flowchart of participant selection and allocation is not clear.
[6] Not all participants consented to additional genotyping.
[7] *n* of reported dropouts does not coincide with the *n* calculated when abstracting participants from the PP analysis from those in the ITT.

FIGURE 2 Included randomized controlled trials investigating the effects of ketogenic therapy on patients with Alzheimer disease or mild cognitive impairment, rated against the Cochrane risk of bias tool (43).

Outcomes of psychological interest included the Geriatric Depression Scale (73) and the Profile of Mood States Bipolar Scale (74), applied by Krikorian et al. (50) and Brandt et al. (45), respectively. The latter study also evaluated efficacy in everyday behavior via the Minimum Data Set for Home Care (75).

Most studies assessed urinary (50) or blood ketone bodies concentrations (47–49, 51–53) in the form of acetoacetate (AcAc) or serum β-hydroxybutyrate (BHB). In the BENEFIC (Brain ENErgy Fitness, Imaging and Cognition) trial (47), positron emission tomography (PET) imaging was applied to assess the cerebral metabolic rate (CMR) of AcAc (CMR_{AcAc}) and ketones ($CMR_{Ketones}$). In the BEAM trial (46), a lumbar puncture was performed pre- and postintervention for the collection of cerebrospinal fluid (CSF) and the assay of Aβ42 and total tau (t-tau) concentrations via INNO-BIA-Alzbio3 fluorimetric immunoassay. In addition, [^{11}C] AcAc brain uptake was evaluated via PET. Finally, Torosyan et al. (54) assessed the regional cerebral blood flow (rCBF) using ^{15}O-water PET scans, by quantifying 47 standardized volumes of interest (sVOI).

The majority of RCTs (45, 47–49, 52–54) assessed the apolipoprotein ε4 allele (*APOE* ε4) status of participants

TABLE 3 Intervention particularities, outcomes, and findings of the included randomized controlled trials assessing the effects of ketogenic therapy on patients with mild cognitive impairment and/or AD[1]

First author	Brandt (45)	Craft (46)	Fortier (47)	Henderson (48)	Henderson (49)	Krikorian (50)	Ota (51)[2]	Rebello (52)	Reger (53)	Torosyan (54)
Intervention	MAD with ≤20 g net CHO (total CHO minus fiber), large amounts of fat to satiety, moderate protein, ample hydration and unrestricted energy intake.	MMKD (<15 g CHO/d)	kMCT drink: emulsion with 12% Captex 355 [60% caprylic acid (8:0), 40% capric acid; Abitec Corp.] in lactose-free skim milk. The drink provided 30 g kMCT in 250 mL (Nalgene).	Powder sachets with 10 g AC1202 (MCT composed of glycerin and caprylic acid, known as tricaprylin/ trioctanoin), mixed with a meal replacement drink (Ensure, Abbott Lab Inc.), taken at breakfast for 7 d, and a double dose thereafter (2 × 10 g AC1202)	2 × powder sachets per day with 10 g AC1202 each (MCT, >95% of the fatty acids being caprylic acid). Product luted in water or other liquids, forming a drink.	Dietary education and counseling for adherence to a KD (5%–10% of calories from protein, <20 g CHO/d), with fruit restriction and a CHO intake based on small portions of vegetables. MUFA was the preferred fat source.	Meal: 50 g ketogenic formula (Ketonformula) containing 20 g of MCTs.	56 g MCTs (MCT oil, Nestlé) added to 6 oz Yoplait 99% fat-free fruit yogurt.	MCTs (40 mL) (Neo-Bee 895, Stepan Inc.), blended with 152 mL heavy whipping cream to form a 690-kcal drink.	40 g caprylidene (MCT) Axona® in capsules (Accera, Inc.).
Comparator	NIA diet: high intake of fruit, whole-gains, fat-free/low-fat dairy, seafood, lean meat, eggs, poultry, oils, beans, peas, vegetable, nuts/seeds. Low intake of sodium, solid fats, refined gains, sugar.	Equicaloric AHAD (<10 g fat/d).	Placebo drink: refined, bleached, winterized, deodorized, high-oleic-acid sunflower oil, as the non-ketogenic lipid.	Powder sachets with 10 g placebo, mixed with a meal replacement drink (Ensure, Abbott Lab, Inc.), taken at breakfast for 7 d, and a double dose thereafter (2 × 10 g placebo).	2 × powder sachets per day, each with 10 g placebo (isocaloric to the active powder, consisting of 51% gum acacia, 37% dextrose, 10% safflower oil, and 2% syloid).	Healthy diet with ≥50% of calories from CHO, high fruit and vegetable intake. MUFA as the preferred fat source.	Meal: isocaloric placebo formula without MCTs.	Placebo (canola oil, color matched) added to 177.4 mL Yoplait 99% fat-free fruit yogurt.	Placebo drink with heavy whipping cream alone (232 mL, 690 kcal).	Placebo capsule.
Intervention duration	12 wk	6 wk	6 mo	90 d	90 d	6 wk	1 meal (single intake), consumed 120 min before tests	24 wk	1 meal consumed 90 min before tests	45 d
Acute intervention	No	No	No	NR[3]	NR[3]	No	✓	✓	✓	✓

(*Continued*)

TABLE 3 (*Continued*)

First author	Brandt (45)	Craft (46)	Fortier (47)	Henderson (48)	Henderson (49)	Krikorian (50)	Ota (51)[2]	Rebello (52)	Reger (53)	Torosyan (54)
Long-term intervention	✓	✓	✓	✓	✓	✓	No[2]	✓	No	✓
Washout duration	N/A	6 wk	N/A	2 wk post-intervention	2 wk post-intervention	N/A	1 visit (NOD)	N/A	1 visit	N/A
Compliance assessment	Urinary ketone levels (intervention) and HEI ≥85 (controls)	Plasma ketone levels	Bottle count, blind blood analyses	Consumption log >80% of intended dose	NR	Diet records evaluated by a dietitian and urinary ketones	N/A (acute intervention only)	By a registered dietitian via daily diet diaries	N/A (acute intervention only)	NR
APOE ε4 status	✓	No	✓	✓	✓	No	No	✓	✓	✓
Adverse events	Minor GI issues and 1 vasovagal episode	NR	Nausea, therapy intolerance, headache, GI issues (diarrhea, reflux, bloating, constipation)	GI adverse events	NR	NR	Diarrhea	GI issues	NR	NR
Primary outcomes	MCS	Δ in CSF levels of Aβ42 and t-tau (INNO-BIA-Alzbio3)	Δ in CMR_{AcAc} and $CMR_{Ketones}$ by PET imaging (Patlak method)	Improvements in cognition (Δ in the ADAS-Cog and ADCS-CGIC)	ADAS-Cog	TMT, V-PAL, GDS	Acute WAIS-III, WMS-R, Stroop, TMT, all at 120 min post-meal	ADAS-Cog, TMT, and Digit Symbol tests	ADAS-Cog, MMSE, Stroop	rCBF (^{15}O-water PET scans) analyzed with sVOI and voxel-based spm
Secondary outcomes	MMSE, MDS-HC, POMS-Bi	Δ in memory composite score, insulin sensitivity, [^{11}C] AcAc PET uptake	CMR_{Glu}, plasma medium-chain fatty acids Cognition: RL/RI-16, MMSE, MoCA, VF, BVMT-R, BNT, TMT, Stroop	MMSE, serum BHB	Serum BHB	Urinary ketone levels, fasting plasma insulin, anthropometry, FPG	Plasma ketone bodies (AcAc and BHB) concentrations	Plasma Glu, insulin, and pre-/post-prandial BHB	BHB	rCBF by sVOI and voxel-based spm
Time points	Baseline, at 3, 6, 9, and 12 wk	Baseline, at 6, 12, and 18 wk	Baseline, end (last wk of mo 6)	Baseline, days 45 and 90	Baseline, days 45, 90, and 104	Baseline and end of intervention (post-6 wk)	Baseline, at 120 min post–meal ingestion	Baseline, weeks 4, 8, 12, 16, and 20	Baseline, 90 min	Baseline (before, after first pill) and on day 45 (before, after final pill)

(*Continued*)

TABLE 3 (*Continued*)

First author	Brandt (45)	Craft (46)	Fortier (47)	Henderson (48)	Henderson (49)	Krikorian (50)	Ota (51)[2]	Rebello (52)	Reger (53)	Torosyan (54)
Results	MCS of the MAD group increased slightly over the trial, whereas in the NIA group it declined slightly (not significantly). MCS and MMSE scores of compliant patients did not differ from baseline. Mood of MAD subjects improved at wk 6.	Global [^{11}C] AcAc uptake increased after the KD intervention. CSF t-tau increased with the KD, with a similar trend noted for Aβ42. Global [^{11}C] AcAc uptake decreased after the low-fat diet. No changes were observed after adoption of the low-fat diet regime.	Brain ketone metabolism increased (230%) in the kMCT group, whereas brain Glu uptake remained unchanged. Episodic memory, language, executive function, and processing speed improved on the kMCT *vs.* baseline. Increased brain ketone uptake was related to several cognitive scales.	AC-1202 elevated serum ketone bodies and improved ADAS-Cog scores compared with the placebo. Effects were most notable in *APOE* ε4(−) subjects. A significant pharmacologic response was observed between serum BHB levels and change in the ADAS-Cog scores in *APOE* ε4(−) subjects, at day 90.	Among *APOE* genotypes, homozygous carriers of the ε3 on AC-1202 had improved cognition relative to placebo. Improved cognition was noted among *APOE* ε4(−) subjects on AC-1202 relative to placebo. Specific genotype combinations of *IDE* and *APOE* ε4(−), and *IL1B* and *APOE* ε4(−) produced more improvements.	The intervention improved secondary memory performance and reduced energy intake and anthropometric parameters. No effect was recorded on the depressive symptoms and the TMT. Ketone levels were positively correlated with memory performance.	The ketogenic formula increased plasma ketone bodies. No differences were noted between scores after taking the ketogenic or the placebo formula, in any cognitive test after correction for multiple testing.	MCT oil intake increased serum ketone bodies and improved memory in the *APOE* ε4(−) participant, whereas intake of placebo did not improve any cognitive measure. In the *APOE* ε4(+) patient an increase in post-prandial serum BHB was noted.	MCT treatment improved ADAS-Cog performance for *APOE* ε4(−) subjects, but not for the (+) ones. Higher ketone levels were associated with greater improvement in paragraph recall among those on MCT treatment.	*APOE* ε4(−) patients had elevated rCBF in the left superior lateral temporal cortex after 45 d of following adopting a caprylidene diet. *APOE* ε4(+) patients did not display changes in rCBF.

[1] AcAc, acetoacetate; AD, Alzheimer disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale (58); ADCS-CGIC, AD Cooperative Study—Clinical Global Impression of Change (76); AHAD, American Heart Association diet; *APOE* (ε4), apoε4 allele; Aβ42, amyloid β 42; BHB, serum β-hydroxybutyrate; BNT, Boston Naming Test (65); BVMT-R, Brief Visuospatial Memory Test-Revised (62); CHO, carbohydrates; CMR, cerebral metabolic rate; CSF, cerebrospinal fluid; FPG, fasting plasma glucose; GDS, Geriatric Depression Scale (73); GI, gastrointestinal; Glu, glucose; HEI, Healthy Eating Index (57); IDE, insulin-degrading enzyme; IL1B, interleukin 1β; KD, ketogenic diet; kMCT, commercially available drink; MAD, modified Atkins diet; MCS, Memory Composite Score (Hopkins Verbal Learning Test-Revised and BVMT-R); MCT, medium-chain triglyceride; MDS-HC, Minimum Data Set for Home Care (75); MMKD, Modified Mediterranean Ketogenic diet; MMSE, Mini-Mental State Exam (59); MoCA, Montreal Cognitive Assessment (60, 64); N/A, not applicable; NIA, National Institute of Aging; NOD, not other defined; NR, not reported; PET, positron emission tomography; POMS-Bi, Profile of Mood States Bipolar Scale (74); rCBF, regional cerebral blood flow; RL/RI-16, Rappel Libre/Rappel Indicé (64); spm, statistical parametric mapping; Stroop, Stroop Color Word Interference (66); sVOI, standardized volumes of interest; TMT, Trail Making Test (68); t-tau, total tau; VF, Verbal Fluency (67); V-PAL, Verbal Paired Associate Learning Test (63); WAIS-III, Wechsler Adult Intelligence Scale-3rd (77); WMS-R, Wechsler Memory Scale-Revised (78).

[2] The study had a double design: a RCT (presented herein) and a longitudinal clinical trial without a comparator (omitted for not fulfilling the inclusion criteria).

[3] Some outcomes were also measured after the first intervention.

from blood samples, by categorizing subjects with ≥1 copy of the *APOE* ε4 gene as *APOE* ε4(+) (45, 54). In the Fortier et al. (47) trial, *APOE* genotyping was performed by real-time PCR (79), while Henderson et al. (48, 49) used allele-specific extension (80). Apart from the *APOE* ε4, Henderson et al. (49) additionally performed genotyping on *APOE* ε2, 3 and single nucleotide polymorphisms (SNPs) in the interleu kin1β (*IL1β* and insulin-degrading enzyme (*IDE*) gene.

Intervention results on cognition

Table 4 summarizes the findings of each intervention. The majority of trials (45, 47–53) assessed the effect of nutritional ketosis on a variety of cognition outcomes. The ketogenic therapy proved successful in improving general cognition using the ADAS-Cog, in both acute (53) and long-term (48, 49, 52) interventions. The MMSE appeared less sensitive to ketogenic treatment, with the Fortier et al. (47) and Brandt et al. (45) RCTs indicating lack of significant improvement, and only 1 trial (48) suggesting ameliorated results posttreatment.

Long-term ketogenic therapy appeared to improve episodic memory as demonstrated by improved scores in the RL/RI-16 and BVMT-R tests (47), as well as secondary memory, assessed via V-PAL (50). However, consumption of a ketogenic formula (51) failed to induce acute improvements in either the WAIS-III, or the WMS-R tests.

As far as executive ability and attention are concerned, none of the included trials revealed either acute (51) or long-term (50, 52) improvements based on the TMT or the Digit Symbol Substitution Test (52). On the other hand, results concerning the Stroop Color Word Interference test appear to be time-dependent, with improved results noted in patients with MCI treated with ketogenic agents for 6 months (47), and nonsignificant changes over a short-term treatment duration (51, 53).

Adherence to a KD failed to improve mood among patients with MCI (45, 50). In parallel, when efficacy in everyday behavior was assessed postintervention, no changes were noted (45). According to the trial performed by Krikorian et al. (50), adherence to a very low carbohydrate diet decreased body weight and waist circumference and ameliorated fasting plasma glucose and insulin concentrations.

Intervention results on ketone bodies production and utilization

Increases in blood ketone bodies concentrations were unanimous in all RCTs, after either acute (51–53) or long-term ketogenic therapy (47, 48). In addition, brain ketone uptake and utilization were also improved, as indicated by global brain CMR_{AcAc}, $CMR_{Ketones}$ (47), and [^{11}C] AcAc (46). In parallel, brain uptake and utilization of glucose appeared to remain unchanged (47). According to Torosyan et al. (54), adherence to ketogenic therapy for 45 days increased rCBF in the left superior lateral temporal cortex.

Effects of intervention according to *APOE* status

In most studies (48, 53), *APOE* ε4(+) participants failed to increase blood ketone concentrations to the same extent as the *APOE* ε4(−) ones. Rebello et al. (52) reported an increase in BHB concentrations among the *APOE* ε4(−) group at baseline; however, at 24 wk the increase was higher among the *APOE* ε4(+) group, indicating an adaptation to the intervention among *APOE* ε4(−) participants. In addition, the BENEFIC (47) and Brandt et al. trials (45) failed to demonstrate differences in the ketosis and cognitive outcomes according to *APOE* status. *APOE* ε4(−) patients exhibited elevated rCBF in the left superior lateral temporal cortex (54) and improved cognition as evaluated with the ADAS-Cog (48, 49, 53).

Overall, ketone bodies concentrations were directly correlated to the neurocognitive batteries including paragraph recall (53), secondary memory performance (V-PAL) (50), TMT (47), BNT, VF (47), and general cognition using the ADAS-Cog (48, 52).

Discussion

The present systematic review indicated that, based on the available RCTs, adherence to a ketogenic therapy appears to induce many cognition-related benefits among adults with MCI and/or AD. In further detail, both the direct administration of ketogenic agents and the use of high-fat, low-carbohydrate ketogenic meals/diets increased serum and brain ketone availability and induced beneficial effects on a variety of neurocognitive outcomes. Among *APOE* ε4(+) and (−) carriers, the effect appears to be higher in the latter than in the former.

Adherence to ketogenic therapy and neurocognition

The present results collectively indicate that adherence to ketogenic therapy among adults with MCI and/or AD improves both acute and long-term cognition. The findings reveal that the effects of ketogenic therapy appear similar, either when delivered acutely (through 1 meal) or over a longer period (months). Ketone availability appears to provide an alternative energy source for the aging brain cells (81–85), both directly, and indirectly via effects on the synaptic transmission and the intrinsic neuronal excitability. The identified pathways explaining the efficacy of the ketogenic therapy include modulation of oxidative stress and inflammatory responses, inhibition of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, attenuation of Aβ-induced mitochondrial alterations and associated toxicity, and activation of the peroxisome proliferator–activated γ receptor (81, 83, 86–88). According to Croteau et al. (89), when MCTs are provided as treatment, all types of MCTs induce similar brain ketone uptake improvements.

When considering the ketogenic therapy narrative, however, one should also take into account that the improved cognition is only apparent when patients with MCI are concerned, because RCTs performed on cognitive-healthy participants failed to manifest further cognitive function improvements, as expected (90).

TABLE 4 Overview of the findings associated with ketogenic therapy in patients with AD or mild cognitive impairment[1]

Effects	First author	Cognitive battery	Mood/depression	Efficacy in everyday behavior	Blood ketone bodies concentrations	AD protein and peptide concentrations in CSF	Brain ketone uptake	rCBF
Long-term	Brandt (45)	∼ MMSE and MCS	↑ POMS-Bi (at wk 6)	∼ MDS-HC				
	Craft (46)					↑ t-tau, ∼ Aβ42	↑ [^{11}C] AcAc	
	Fortier (47)	∼ MMSE and MoCA, ↑ Stroop,↑ RL/RI-16, ↑ BVMT-R			↑ BHB		↑ Global brain CMR_{AcAc} and $CMR_{Ketones}$ ∼ CMR_{Glu}	
	Henderson (48)	↑$^{\varepsilon4-}$ ADAS-Cog, ↑$^{\varepsilon4-}$ ADCS-CGIC (day 45), ↑$^{\varepsilon4+}$ MMSE (day 104)			↑ BHB			
	Henderson (49)	↑[2] ADAS-Cog ↑$^{\varepsilon4-}$ ADAS-Cog						
	Krikorian (50)	∼ TMT, ↑ V-PAL	∼ GDS					
	Rebello (52)	↑$^{\varepsilon4-}$ADAS-Cog,[3] ∼ TMT and Digit Symbol						
	Torosyan (54)							↑$^{\varepsilon4-}$ rCBF in the left superior lateral temporal cortex
Acute	Ota (51)	∼ WAIS-III, WMS-R, Stroop, TMT			↑ AcAc and BHB			
	Rebello (52)				↑$^{\varepsilon4-}$ BHB[3]			
	Reger (53)	↑$^{\varepsilon4-}$ ADAS-Cog, ∼ Stroop			↑ BHB			
	Torosyan (54)							↑$^{\varepsilon4-}$ rCBF in dorsolateral prefrontal and temporal cortices

[1] AcAc, acetoacetate; AD, Alzheimer disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale (58); ADCS-CGIC, AD Cooperative Study–Clinical Global Impression of Change (76); *APOE*, apoE; Aβ42, amyloid β 42; BHB, serum β-hydroxybutyrate; BVMT-R, Brief Visuospatial Memory Test-Revised (62); CMR, cerebral metabolic rate; CSF, cerebrospinal fluid; GDS, Geriatric Depression Scale (73); Glu, glucose; MCS, Memory Composite Score; MDS-HC, Minimum Data Set for Home Care (75); MMSE, Mini-Mental State Exam (59); MoCA, Montreal Cognitive Assessment (60); POMS-Bi, Profile of Mood States Bipolar Scale (74); rCBF, regional cerebral blood flow; RL/RI-16, Rappel Libre/Rappel Indicé (64); Stroop, Stroop Color Word Interference (66); TMT, Trail Making Test (68); t-tau, total tau; V-PAL, Verbal Paired Associate Learning Test (63); WAIS-III, Wechsler Adult Intelligence Scale-3rd (77); WMS-R, Wechsler Memory Scale-Revised (78); $^{\varepsilon4-}$, *APOE* ε4(−); $^{\varepsilon4+}$, *APOE* ε4(+); ↑, improved; ∼, no change.

[2] Homozygous carriers of the ε3 allele.

[3] $n = 1$ participant only.

Glucose metabolism and cerebral substrate use post-intervention

Long-term adherence to ketogenic therapy does not appear to affect glucose metabolism in a negative manner (47, 50, 52). The BENEFIC trial (47) showed that cerebral glucose uptake remained unchanged after 6 mo of ketogenic therapy, whereas Rebello et al. (52) reported normal blood glucose and insulin concentrations after 24 wk consuming yoghurt with MCT oil every day. Thus, the availability of glucose and the insulin response appear unaffected. In parallel, Krikorian et al. (50) reported ameliorated fasting glucose and insulin concentrations 6 wk postintervention, as a possible epiphenomenon of the observed reduction in body weight and waist circumference of participants. After all, low-carbohydrate diets appear promising for both diabetes treatment and weight loss (91–93). On the primary prevention level, the risk of developing AD is increased when a trend toward insulin resistance is observed among older adults (94, 95). Based on the RCTs included in the present systematic review, and individual case studies (96), the use of ketoneurotherapeutics can improve the glycemic profile, which in turn, by inference, might delay progression to AD.

Although the low glucose uptake of the aging brain has long been identified in AD (97, 98) and has been associated with cognitive decline (99, 100), very few AD-related therapies have focused on addressing the issue of the induced energy availability (101, 102). Based on the CMR and [^{11}C] AcAc PET uptake, ketogenic interventions increased brain ketone metabolism (46, 47) and this produced subsequent increments in the total brain metabolism as indicated by the sVOI and voxel-based spm (54). These findings suggest that the metabolism gap observed during AD progression as a result of reduced brain glucose availability (103) is compensated for by the increased utilization of ketones. Ketones serve as alternative substrate sources for the brain, a "super fuel," preventing energy starvation (91, 103–105). Thus, ketones seem to be an obligatory brain substrate among persons with MCI, owing to the low net cerebral glucose uptake (103).

Ketogenic therapy according to *APOE* status

With the suggested etiology of AD being a complex interplay of genetic and environmental causes, genome-wide association studies have revealed many genes associated with increased risk of AD development (106–114). Among those, the *APOE* gene is a major genetic risk determinant for the development of sporadic late-onset AD (115, 116). Moreover, the *APOE* ε4 variant has been suggested to affect the clearance capacity and degradation of β-amyloid from the brain, CMR, cholesterol transport, glucose metabolism, β deposition, as well as tau pathology and degeneration (28, 117–120).

In general, ketone concentrations were directly correlated to the neurocognitive battery (47, 48, 50, 53), indicating a dose–response association (48). This effect was significant among the *APOE* ε4(−) subjects and the total sample; however, it was missing from the *APOE* ε4(+) participants (48). Owing to the aforementioned dose–response association, an important prerequisite for this effect was that participants were intervention-compliant (48). In addition, a time frame was suggested by Henderson et al. (48) for the results to become efficient. In greater detail, the significant pharmacologic response of the ketogenic intervention among *APOE* ε4(−) participants was initiated 90 d post-administration (48). Torosyan et al. (54) showed that adherence to the ketogenic therapy increased rCBF in the left superior lateral temporal cortex, as indicated by the sVOI, corroborated by the spm. Based on the spm, the long-term increase in rCBF was noted in the anterior cerebellum, left inferior temporal cortex, and hypothalamus. When more genes and loci were analyzed (49), improvements in cognition outcomes were more significant among the ε3/ε3 genotype group, and specific genotype combinations of *IDE* (heterozygous C/T for *IDE rs2251101SNP*) and ε4(−) produced similar positive outcomes. In addition, specific genotype combinations of *IL1B* (homozygous for T/T for *IL1B rs1143627* and homozygous for the C/C allele of *rs16944*) and ε4(−) resulted in additive cognition improvements post-intervention.

However, it should be noted that *APOE* ε4(+) participants did not fail to respond to the treatment. The effect of ketogenic therapy on *APOE* ε4(+) participants appears delayed, with 1 trial showing improvement in the MMSE score on day 104 compared with the controls (48). On the other hand, Torosyan et al. (54) failed to indicate regions of increased rCBF among *APOE* ε4(+) participants; however, the trial lasted for a total of 45 days, a duration much shorter than the cutoff suggested by Henderson et al. (48) as the time frame needed for induction of a significant response among *APOE* ε4(+) participants. In parallel, Torosyan et al. (54) failed to assess the degree of compliance to the therapy among participants; thus, a high prevalence of noncompliance might have diminished the expected response further.

Most trials demonstrated differences in the blood ketone concentrations, ketone uptake, and cognition outcomes postintervention among participants with *APOE* ε4(−) or *APOE* ε4(+) status. However, 4 RCTs failed to reveal such differences (45, 47, 52, 53). The trial by Rebello et al. (52) was extremely underpowered and lacked statistical analyses, because it included only 2 participants in the intervention group, 1 being *APOE* ε4(−) and the other *APOE* ε4(+). On the other hand, the BENEFIC (47) and Brandt et al. trials (45) were also underpowered. In parallel, the lack of differences reported in the Rebello et al. (52) and Reger et al. (53) trials can also be attributed to the delayed response suggested to occur among *APOE* ε4(+) participants. Given that both trials assessed the effects of a short-term intervention, it is possible that the trial duration was inadequate for *APOE* ε4(+) subjects to respond adequately.

Effects of ketogenic therapy on t-tau and Aβ42 CSF concentrations

Concerning other AD biomarkers like t-tau and Aβ42 concentrations, an increase in CSF t-tau and a trend toward an increase in Aβ42 were reported after a KD

(46). However, research appears conflicting regarding the relation of these biomarkers with cognitive decline (121). Some researchers (122, 123) have reported increased CSF Aβ42 concentrations, whereas others have suggested reduced concentrations, among patients with cognitive decline (124–126). According to Lee et al. (121), although the aggregation of tau and Aβ isoforms is typical in AD, research attempting to establish their reliability as biomarkers has produced contradictory results. CSF t-tau and Aβ isoforms, in particular, rely on insufficient analytical standardization and are not AD-specific biomarkers; however, they are often used as proxy biomarkers for detecting changes in AD degeneration (121). Overall, CSF Aβ42 concentrations tended to correlate well with brain Aβ content (127). However, fluctuations, especially concerning t-tau, have been recorded in acute disorders, and the invasive nature of a lumbar puncture might also affect the results via the induced pain, stress, and possible CSF contamination. However, differences in the results associated with increased AD risk might be attributed to the fact that these biomarkers are not so accurate among patients in the prodromal stages of AD (121), as most patients included in the present systematic review were. Subsequently, it is difficult to interpret the findings of the Craft et al. trial (46), especially given the small number of participants and the fact that *APOE* status was not assessed, although carriers have been shown to carry a higher amyloid burden (128, 129). In parallel, the literature is still too limited to discern whether ketogenic therapy entails antiamyloid effects or just cognition benefits for patients with MCI/AD.

Research in the pipeline

The need for effective MCI remedies has created an upsurge in ketogenic therapy research, with a plethora of additional outcomes being examined (31, 55). During the search process, protocols of ongoing RCTs were identified meeting the review's criteria, without having published any results yet (**Table 5**). A total of 4 ongoing parallel RCTs were identified in clinicaltrials.gov, comparing adherence to a KD, a modified Mediterranean KD, consumption of ketogenic drinks, or MCT oil against other diet regimes, placebo drinks, or lower intake of MCT oil among patients with MCI/AD. The MCT and brain Metabolism in Alzheimer's disease (MCT-MA) trial (NCT02709356) appears to have completed the intervention and results are expected. In the MINT-01 (Medium-chain triglyceride INTervention for patients with Alzheimer disease) RCT (NCT02912936), the intervention was completed in December 2019. The TDAD (Therapeutic Diets in Alzheimer's Disease) (NCT03860792) and BEAT-AD (Brain Energy for Amyloid Transformation in Alzheimer's Disease) (NCT03472664) trials are expected to publish results after the year 2023. Once more, although important for AD research, the reported primary outcomes are heterogeneous, with only 1 trial reporting the assessment of cognitive ability postintervention.

In addition, after the present search was completed, the BEAM trial (46, 55, 56) published another full-text publication (130) during early 2020, based on the same protocol. The results revealed that adherence to a modified Mediterranean KD increased cerebral perfusion and ketone body uptake.

Limitations of the present study

The present systematic review accrued the best available evidence (i.e., from RCTs) on the effects of ketogenic therapy on patients with AD/MCI. Important shortcomings of the included trials involve the relatively small sample sizes used in the majority of RCTs, as well as the lack of compliance assessment. In addition, as Tolar et al. noted (129), patient heterogeneity is often common in MCI RCTs owing to the coexistence of distinct neuropathologies resulting in increased variability in the induced biomarker changes and the cognitive decline of participants, and, in parallel, *APOE* status is not always considered in AD research. However, treatment responses appear mediated by *APOE* status. Inarguably, as for every systematic review, the present review also inherits all the limitations of its included trials, namely the increased RoB demonstrated by the RoB assessment and the low methodological quality. On these premises, it was difficult to meta-analyze extracted data, and, for this, future studies with specific designs and outcomes are required.

A holistic view of the available RCTs applying ketogenic therapy to patients with MCI and/or AD also indicates a high degree of heterogeneity in the study design and methodology of the published research. Induction of ketosis was not always measured or achieved (50), despite the study protocols. A variety of agents and methods were applied to increase ketone bodies production, using both short- and long-term interventions, not allowing for the synthesis of the results. According to Margolis and O'Fallon (132), exogenous ketone supplementation, as in the form of MCT or ketogenic agents, consists of an alternative strategy aiming to increase ketone bodies concentrations, while reducing possible adverse events associated with adherence to a KD.

Admittedly, however effective it may be, the KD is not an "easy" diet regime. Compared with the other "healthy" diets, it is restrictive (129), and its initiation is often associated with adverse gastrointestinal events and hypoglycemic episodes (133). According to Taylor et al. (134), the KD can be nutritionally dense, while meeting the RDAs of older adults. However, adherence to the KD requires drastic changes, and, for this, long-term compliance is challenging to maintain (135). For all these reasons, the duration of the majority of interventions did not appear to exceed 6 mo.

Conclusions

Currently, there are no approved drugs to delay or halt the progress of cognitive decline in AD (124). Although faith in the therapeutic effects of the KD was initially attributed to Hippocrates (136), research on ketoneurotherapeutics for AD appears young. The results underline that, collectively, the efficacy of ketogenic therapy in MCI/AD appears promising, indicating that it is more than a symptomatic remedy

TABLE 5 RCTs in the pipeline, investigating the use of ketogenic diet/agents on patients with Alzheimer disease or mild cognitive impairment[1]

Clinical trial identifier	Study	Collaborators	Design	Intervention/ comparator duration	Intervention	Comparator	Estimated study duration	Primary outcomes	Secondary outcomes
NCT03860792	TDAD[2]	*1*) University of Kansas Medical Center *2*) NIA	Parallel, single-blind (outcomes assessor) RCT	3 mo	KD (1:1) (70% fat, <10% CHO, and 20% protein)	TLC diet (20%–35% fat, 50%–60% CHO, and ∼15% protein as energy. Fat intake is comprised of <7% SFA, ≤20% MUFA, and ≤10% PUFA as total energy. Consumption of ≤200 cholesterol mg/d, ≥2 servings of fruit and ≥5 servings of vegetables daily).	October 2019 to November 2023	*1*) ADAS-Cog *2*) MMSE *3*) Logical memory test (WMS-R) *4*) Stroop *5*) CDR	*1*) Cerebral NAA concentration *2*) Blood platelet mitochondrial function *3*) Self-reported symptoms *4*) Blood ketone concentrations *5*) Days positive for urinary ketones *6*) Dietary intake
NCT02912936	MINT-01[2]	*1*) University of British Columbia *2*) Université de Sherbrooke	Parallel RCT with quadruple masking	10 d	Ketogenic MCT drink (lactose-free skim milk drink containing 25 g MCT oil per 250 mL).	Placebo drink (lactose-free skim milk drink containing high-oleic sunflower oil with the equivalent amount of energy as the active arm).	September 2016 to December 2019	*1*) Adverse events *2*) Plasma ketone concentrations in ascending MCT dose	*1*) AUC of MCT *2*) Δ in cerebral metabolic rate of glucose, blood flow, and MRS after a ketogenic drink *3*) Physical activity
NCT03472664	BEAT-AD[3]	*1*) Wake Forest University *2*) NIA	Parallel, double-blind RCT	4 mo	Modified Mediterranean KD (low-CHO/high-fat diet) including extra virgin olive oil, fish, lean meats, <20 g CHO/d, and a daily MV tablet.	AHA diet (low fat/high CHO). Diet includes fat intake <40 g/d, fruits, vegetables, CHO, adequate fiber, and a daily MV tablet.	July 2018 to April 2023	*1*) CSF Aβ42	*1*) CSF Aβ42/tau *2*) PACC *3*) Cerebral blood flow with ASL

(*Continued*)

TABLE 5 (*Continued*)

Clinical trial identifier	Study	Collaborators	Design	Intervention/ comparator duration	Intervention	Comparator	Estimated study duration	Primary outcomes	Secondary outcomes
NCT02709356	MCT-MA[4]	*1)* Université de Sherbrooke *2)* Fondation Vitae	Parallel,[5] single-blind (patients) RCT	1 mo	Supplementation of caprylic acid MCT oil [60% capric acid (10:0) + 40% caprylic acid] per day.	Supplementation of 30 g MCT oil (100% caprylic acid) per day.	October 2015 to February 2018	*1)* Brain glucose uptake *2)* Brain AcAc uptake	NR

[1]AcAc, acetoacetate; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale (58); AHA, American Heart Association; ASL, arterial spin labeling; Aβ42, Amyloid β 42; BEAT-AD, Brain Energy for Amyloid Transformation in Alzheimer's Disease; CDR, Clinical Dementia Rating (70); CHO, carbohydrates; CSF, cerebrospinal fluid; KD, ketogenic diet; MCT, medium-chain triglyceride; MCT-MA, Medium Chain Triglycerides and brain Metabolism in Alzheimer's disease; MINT-01, Medium Chain Triglyceride INTervention for patients with Alzheimer disease; MMSE, Mini-Mental State Exam (59); MRS, magnetic resonance spectroscopy; MV, multivitamin; NAA, N-acetylaspartate; NIA, National Institute on Aging; NR, not reported; PACC, Preclinical Alzheimer Cognitive Composite (Free and Cued Selective Reminding Test, Logical Memory IIa, Digit Symbol Substitution Test, MMSE); RCT, randomized controlled trial; TDAD, Therapeutic Diets in Alzheimer's Disease; TLC, Therapeutic Lifestyle Changes (131); WMS-R, Wechsler Memory Scale-Revised (78).
[2]RCTs not yet recruiting.
[3]RCTs with a "recruiting" status on www.clinicaltrials.gov.
[4]"Completed" RCT status.
[5]Registration indicates parallel design; however, the explanation of the procedures denotes a crossover intervention.

(137). Nevertheless, research is still scattered and heterogeneous in terms of study design, intervention, participants, and outcomes of interest. Predefining a set of important outcomes for relevant RCTs would add weight to the evidence and aid toward the development of recommendations advocating for the usefulness of ketogenic therapy in AD. Thus, apart from reviewing the available RCTs assessing the efficacy of ketoneurotherapeutics on AD, the present study can also serve as a primer for the design of future clinical trials, to support public health translation and promote the KD as an evidence-based AD prescription remedy.

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