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CLINICAL TRIAL REPORT

Addressing Pain Using a Mediterranean Ketogenic Nutrition Program in Older Adults with Mild Cognitive Impairment

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Abstract: Chronic pain has negative physical and cognitive consequences in older adults and may lead to a poorer quality of life. Mediterranean ketogenic nutrition (MKN) is a promising nonpharmacological intervention for pain management, but long-term adherence is challenging due to the carbohydrate restrictive diet regimen. The main objective of this study was to evaluate the effects of the pilot MKN Adherence (MKNA) Program on pain in older adults with mild cognitive impairment and to assess whether improvements in self-reported pain were associated with adherence to MKN. Older adults (N = 58) aged 60–85 with possible mild cognitive impairment were randomized to a 6-week MKNA arm or an MKN Education (MKNE) program arm. Both arms received the same nutrition education and group format; however, the MKNA arm received additional motivational interviewing and cognitive behavioral skills to enhance adherence. Changes in self-reported pain (Brief Pain Inventory, Roland Morris, Patient's Global Impression of Change) and adherence to MKN (ketone levels, self-reported adherence) were assessed at baseline, 6-weeks, and 3-months post intervention. Both arms showed clinically significant reductions in pain. Greater adherence to MKN across the 6-week intervention was associated with higher ratings of pain-related changes on the Patient's Global Impression of Change scale. Based on these findings, adherence to MKN may promote improvements in self-reported pain in older adults with mild cognitive impairment and findings support the need for future full-scale randomized clinical trials evaluating MKN programs on pain. Trial Registration: Clinicaltrials.gov ID: NCT04817176

Keywords: ketogenic diet, ketosis, chronic pain, adherence, nutrition program

Introduction

Studies suggest that over 50% of older adults report bothersome pain.[1] Chronic pain may lead to accelerated cognitive decline and increased risk of dementia.[2–4] Unfortunately, older adults may be at increased risk for adverse side-effects from pain medications, which can lead to injuries, an increased risk of hospitalization, and a poor quality of life.[5,6] Nonpharmacological interventions offer a promising alternative for pain management in older adults.[7] As the aging population in the United States is expected to more than double by 2050, chronic pain will become a more serious problem in older adults with cognitive impairment.[8] Thus, there is an imperative need to develop scalable behavioral interventions for pain designed for older adults with cognitive concerns.

A recent systematic review reported an association between chronic pain and an increased risk of cognitive decline and dementia.[9] Van der Leeuw et al[2] discovered that older adults with higher levels of pain had an increased risk of developing major memory impairment. Furthermore, a 2-year longitudinal study reported an association between persistent pain and an increased risk of dementia and accelerated cognitive impairment.[3] Overall, these studies suggest that chronic pain has the risk of negative physical and cognitive consequences in older adults. One potential mechanism that may link chronic pain and Alzheimer's disease, the most common neurodegenerative disorder, is neuroinflammation.[10,11] For example, neuropathic pain in pre-clinical models activates microglia in the central nervous system, which in turn promotes neuroinflammation.[10,12]

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A review on the role of neuroinflammation on neurodegenerative disorders reported that pro-inflammatory responses, such as activation of cytokines, are associated with accelerated progression of neurodegenerative diseases such as Alzheimer's disease.[11] Given the link between chronic pain and cognitive decline, pain management interventions that target neuroinflammation in older adults with mild cognitive impairment may prove beneficial.

Chronic pain management in older adults commonly includes pharmacological treatments, physical therapy, and other interventions.[13] Factors such as polypharmacy, changes in pharmacokinetic functions, and adverse side effects should be considered in the pharmacological management of pain in older adults.[14] Pain medications are especially problematic in older adults and may give rise to adverse reactions such cognitive impairment.[5] Thus, nonpharmacological interventions may offer a lower risk alternative to pain medications in older patients. A recent systematic review reported that nondrug interventions such as exercise and acupressure were highly effective in the management of pain in older adults in long-term care.[7] Furthermore, nonpharmacological interventions such as hypnosis, acupuncture, and natural sounds reduced pain intensity for participants in an intensive care unit.[15] Nutrition is also a promising nonpharmacological intervention that has shown benefits for pain. For example, a recent systematic review reported that dietary interventions with antioxidant and anti-inflammatory effects reduced pain intensity in patients with chronic low back pain and alleviated pain symptoms in patients with neurological disorders.[16] These studies suggest that nonpharmacological interventions offer a safer alternative to pain medications and may be used to improve chronic pain in older adults.

Ketogenic nutrition is a promising nonpharmacological intervention and has demonstrated benefits for pain in animal and human studies. For example, a recent animal study assessed inflammatory and spontaneous pain in rats and mice in a KN group or a control laboratory rodent diet group.[17] The KN intervention led to a reduction in inflammatory pain in both species and reduced spontaneous pain in rats.[17] Furthermore, a randomized human clinical trial found improvements in average weekly pain and pain interference in middle-aged adults who completed a whole-food ketogenic diet intervention.[18] It is noteworthy that the intervention included the removal of ultra-processed foods, which may lead to additional benefits for pain.[18] Additionally, a pilot study examined the effects of KN on pain in patients with lipedema, a condition that commonly leads to excess body weight and pain.[19] The 7-week ketogenic diet intervention led to a significant reduction in perceived pain measured using the visual analog scale.[19] A recent systematic review reported that anti-inflammatory diets such as the Mediterranean and ketogenic diet led to significant improvements in pain for patients with rheumatoid arthritis.[20] The review also found greater improvements in pain for studies with longer dietary interventions.[20] A retrospective cohort study assessing the effects of a Mediterranean diet on pain in older adults found an association between higher levels of adherence to the Mediterranean diet and greater improvements in pain severity.[21] These studies suggest that adherence to both Mediterranean and ketogenic nutrition may offer benefits for pain.

Motivational interviewing (MI) and behavior change techniques (BCTs) can improve adherence to lifestyle change programs.[22,23] MI is an evidence-based approach used to positively change behaviors in healthcare and social settings and is associated with higher levels of long-term adherence in older adults.[24,25] Behavior change techniques (BCTs) are used to change target behaviors and have led to positive behaviors and clinically significant benefits in nutrition interventions.[26,27] Given these findings, a nutrition program using combined MI and BCT strategies that promotes behavior change may lead to higher levels of adherence to MKN and greater improvements in pain.

The purpose of this secondary analysis of an early phase clinical trial was to evaluate the effects of an MKN Adherence (MKNA) Program on self-reported pain in older adults with possible mild cognitive impairment. Given the small sample size of the early phase clinical trial, we were primarily interested in evaluating clinically, rather than statistically, significant associations. This approach is consistent with recommendations for early phase clinical trials.[28] We hypothesized that clinically significant improvements in pain would be associated with higher adherence to MKN across arms, and the MKNA Program would promote greater improvements in pain compared to the MKN Education program. As an exploratory aim, we evaluated whether the association between adherence to MKN and improvements in pain may depend on factors such as weight loss, sleep, mood, or blood glucose levels.

Methods

Participants

Participants aged 60–85 with possible mild cognitive impairment were recruited from the Florida State University SeniorHealth™ Clinic and the community to participate in the pilot randomized clinical trial. Exclusion and inclusion criteria for all study participants are reported in Sheffler et al.[29] Informed consent was obtained for all eligible participants prior to beginning the clinical trial and the study complies with the Declaration of Helsinki. Additional inclusion criteria were added to the clinical trial to recruit a subsample of participants with self-reported pain. Specifically, of the total 58 participants enrolled in the study, a subsample of at least 20 patients were selected based on self-reported pain of 3 or greater in the previous week at screening using a scale of "0=No pain" to "10=Pain as bad as you can imagine" from the Roland-Morris pain scale administered at screening.[30] See Sheffler et al[29] for a CONSORT diagram of the full feasibility pilot trial and detailed description of the study methods. Below we have included a CONSORT diagram for recruitment of the pain sample (see Figure 1).

Design and Procedure

This study reported quantitative findings from a pilot randomized clinical trial to assess the effects of a Mediterranean Ketogenic Nutrition Adherence Program on self-reported pain in older adults with mild cognitive impairment. The study was

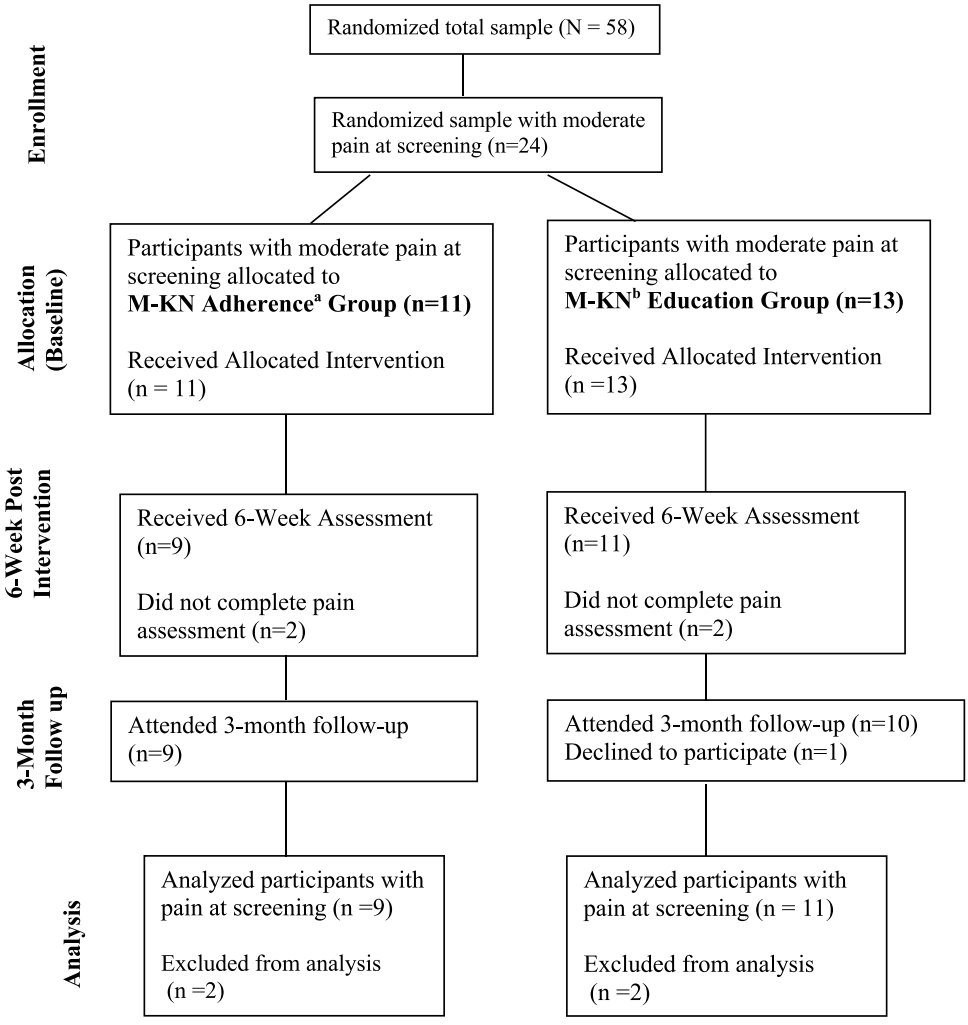

Figure 1 Consort Diagram of Pain Sample in the MI-CBT Ketogenic Nutrition Adherence Program Pilot Trial.
Notes: [a]M-KN Adherence: Mediterranean Ketogenic Nutrition Adherence Program using Motivational Interviewing and Cognitive Behavioral Therapy techniques; [b]M-KN: Mediterranean Ketogenic Nutrition Program Only.

conducted at the Center for Translational Behavioral Research at the Florida State University (FSU) and was approved by the FSU Institutional Review Board. The clinical trial began on September 24, 2021, and was completed on July 1st, 2023. All participants (N = 58) were randomly assigned to the MKNA Program (n = 29) or MKNE Program (n = 29). Both groups received seven 1-hour virtual group meetings via HIPAA-compliant zoom across 6 weeks (two meetings in week 1). Each meeting was led by a licensed psychologist and nurse practitioner with expertise in functional medicine. During the first week of the intervention, both groups attended two sessions that introduced Mediterranean Ketogenic Nutrition (MKN), how to track macronutrients, and how to use the program resources (eg, recipes, informational handouts, individualized calculators). In weeks two through six, all participants were asked to attend weekly sessions to learn about topics related to MKN, eating healthy on a budget, and trouble-shooting questions about the diet. Participants were provided weekly with individualized gram recommendations for fats, proteins, and carbohydrates based on their age, sex, BMI, and activity level. Each week, these individualized recommendations were titrated into a ketogenic ratio – participants began at a 50% fat, 25% protein, and 25% carbohydrate ratio and titrated up to a 70% fat, 25% protein, and 5% carbohydrate ratio. Participants in both arms received a workbook with MKN recipes and informational handouts. Participants in the MKNA arm received additional activities and group discussions using MI-BCT strategies and worksheets (eg, goal setting, problem-solving, and overcoming obstacles). See Sheffler et al[29] for a detailed description of the study design and procedure. Of note, participants were not explicitly told of the minor differences between the arms at baseline in order to reduce potential placebo effects.

Participants in both arms completed weekly online surveys that assessed weekly pain intensity, adherence to MKN, body weight, and mood. Additionally, participants completed daily at-home urine ketone testing and tracked daily macronutrient intake using food logs. The in-person assessments were completed at baseline, at 6-weeks (final week of intervention), and 3-months post-intervention. Self-reported pain assessments administered during in-person visits included the Brief Pain Inventory (BPI), Roland-Morris Pain and Disability Questionnaire (RMDQ), and the Patients' Global Impression of Change (PGIC) scale. Health assessments included blood draws to measure blood glucose levels and other metabolic biomarkers, urinalysis testing to measure ketone levels, and a scale to measure body weight. Additionally, self-report assessments were administered to measure adherence to MKN, mood, and sleep quality.

Measures

The primary outcomes assessed in this study were *pain intensity*, or the "magnitude of experienced pain" and *pain interference*, or the degree at which pain interferes with daily activities such as physical, social, and emotional activities,[31,32] and *patient global impression of change in pain*. Pain intensity and pain interference were measured using the Brief Pain Inventory (BPI), a 17-item questionnaire adapted from Cleeland.[33] A study assessing the validity of the BPI reported the tool to be valid for measuring chronic, nonmalignant pain and found that the tool reflects improvement in pain over time.[34] Previous studies reported that a 30–35% improvement from baseline to the end point or an effect size of 0.5 SD demonstrated a clinically significant difference for pain measures using the BPI.[35–37] The BPI was completed by participants at baseline, 6-weeks, and 3-months post-intervention.

Pain Measures

Pain Intensity

Pain intensity was measured using 4 items in the BPI with possible responses ranging from "0=No Pain" to "10=Pain as Bad as You Can Imagine." Items included pain experienced "at its worst in the last 24 hours" and "pain on average" which were used to measure the magnitude of pain experienced by participants. Pain intensity was calculated as the mean of the 4 items in the BPI with total scores ranging from 0–10 and higher scores indicating worse pain intensity. Changes in pain intensity was calculated by subtracting the 6-week or 3-month total pain intensity score from the baseline pain intensity score, with a higher negative value indicating greater improvement in pain intensity over time.

Pain Interference

Pain interference was measured using 7 items in the BPI, which asked participants to describe how pain interfered with areas such as general activity, mood, and relationships with others "during the past 24 hours." Responses ranged from "0=Does Not Interfere" to "10=Completely Interferes." Pain interference was calculated as the mean of the 7 items in the BPI with total

scores ranging from 0–10 and higher scores indicating worse pain interference. Changes in pain interference over time was calculated by subtracting the 6-week or 3-month total pain interference score from the baseline pain interference score, with a higher negative value indicating greater improvement in pain interference over time.

Patients' Global Impression of Change (PGIC)

The PGIC adapted from Hurst and Bolton[38] is a 7-point scale that asks patients to describe their overall impression of change "related to their painful condition." Responses ranged from "0=No Change (or condition has got worse)" to "7=A great deal better, and a considerable improvement that has made all the difference." A previous study assessing the validity of the PGIC in a real-life setting reported the tool to be a clinically relevant assessment tool.[39] The PGIC was used to evaluate participants' beliefs about changes in their pain after completing the MKN intervention (MKNA Program or MKNE Program). The PGIC assessment was completed by participants at 6-weeks and again at 3-months post-intervention.

Disability

The Roland Morris Disability Questionnaire (RMDQ) adapted from Roland and Morris[30] is a 25-item questionnaire that assesses disability in patients with pain. Pain-related disability was measured using 24 items with total scores ranging from 0 to 24 and higher scores indicating more pain-related disability. Items (Ex: I stay in bed most of the time because of my pain") asked participants if their pain impacted them in the past week with responses including "1=Yes and 0=No". Pain intensity was also measured using 1 item from the RMDQ questionnaire. The item asked participants to rate their level of pain in the past week using a scale of "0=No pain" to "10=Pain as bad as you can imagine." Brouwer et al[40] found that the RMDQ has good reliability for measuring pain in patients with chronic low back pain. The RMDQ was completed by participants at baseline, 6-weeks, and 3-months post-intervention. A 30% reduction from baseline was found to be a clinically significant difference in the RMDQ.[41]

Health Measures

Adherence (Ketosis)

Ketone levels were used as a measure of adherence to MKN. Ketones were measured using at-home urinalysis test strips daily throughout the 6-week intervention and during in-person assessments at baseline, 6-weeks, and 3-months post intervention. Previous studies assessing urinalysis testing for ketones found high sensitivity in tests when the reading was above negative but low specificity.[42] Reported ketone levels included "negative" (0 mg/dL), "trace" (>5 mg/dL), "small" (>15 mg/dL), "moderate" (>40 mg/dL), and "large" (>80 mg/dL). Total ketone levels across the 6-week intervention were calculated by summing days above trace levels of ketones.

Change in Weight

Body weight was recorded in pounds using a scale during in-person assessments at baseline, 6-weeks, and 3-months post intervention. Participants were also asked to record their weight in weekly online surveys. Changes in weight were calculated from baseline to 6-weeks and from baseline to 3-months post intervention.

Blood Glucose

Blood glucose levels (BGL) were measured using fasting blood draws (~10 hours) and were analyzed in the Piccolo Xpress chemistry analyzer during in-person assessments at baseline, 6-weeks, and 3-months post intervention. BGLs analyzed using the Piccolo Xpress ranged from 73 to 134 mg/dL at baseline.

Behavioral Measures

Self-Reported Adherence

Self-reported adherence to MKN was measured weekly using an online questionnaire. Participants were asked to rate how well they felt that they adhered to the diet since the last meeting with responses ranging from "0=Not at all" to "10=Very consistent." Total adherence to MKN across the 6-week intervention was calculated by summing the weekly adherence ratings. Self-reported adherence was also measured during in-person assessments at 6-weeks and 3-months post intervention.

Sleep Quality

Participants were asked to rate their sleep quality using the Pittsburgh Sleep Quality Index (PSQI) adapted from Buysse.[43] The PSQI is a 19-item questionnaire that assesses 7 components of sleep including sleep quality, sleep duration, and sleep efficiency.[43] Subjective sleep quality was assessed in 1 item ("During the past month, how would you rate your sleep quality overall?") with responses ranging from "1=Very Good" to "4=Bad." Participants completed the PSQI assessment during in-person visits at baseline, 6-weeks, and 3-months post intervention.

Mood

The Patient Health Questionnaire (PHQ-9) adapted from Kroenke et al[44] is a 9-item questionnaire that measures the severity of depression and is commonly used to assess depression symptoms. The PHQ-9 asked participants to describe how often they have been bothered by problems in the last 2 weeks such as "little interest or pleasure in doing things" or "feeling down, depressed, or hopeless." Responses ranged from "0=Not at all" to "3=Nearly Every Day" and total scores ranged from "0=minimal depression" to "10=moderate depression" at baseline. Participants completed the PHQ-9 assessment during in-person visits at baseline, 6-weeks, and 3-months post intervention.

Analysis

The data were stored in REDCap and analyzed using IBM SPSS Statistics Version 27.[45] Analyses were conducted for the subsample of patients who reported pain of 3 or greater on the RMDQ at screening (n = 24) and for the full sample (N = 58). Independent sample t-tests were used to compare demographic, pain, behavioral, and health characteristics at baseline between the MKNA and MKNE arms. Pearson correlation analyses were used to determine a relationship between adherence to MKN and changes in pain across both arms. Repeated measures ANCOVA was used to determine changes in reported pain intensity and pain interference before and after the MKN intervention across and between arms. The results focus on analyses completed on a subsample of participants reporting pain ≥3 at screening, while some results of the full sample are reported in tables to assess relationships in a larger sample.

Results

Demographics and Baseline Characteristics

Twenty-four participants reported pain of 3 or greater on a scale of 0–10 on the RMDQ at screening. Of those with moderate pain at screening, 11 participants were assigned to the MKNA arm, and 13 participants were assigned to the MKNE arm. The average age of participants in the MKNA group was 73%, and 82% of the participants (n = 9) were female. The average age of participants in the MKNE group was 75.1%, and 69% of the participants (n = 9) were female. Independent sample t-tests were used to assess differences in baseline demographics, pain, and health characteristics between groups. There were no significant differences between the MKNA arm and MKNE arm for age, sex, pain intensity, pain interference, pain-related disability, ketones, glucose, weight, sleep quality, or depressive symptoms (see Table 1). Some participants reported pain intensity and pain interference less than 3 out of 10 on a numerical rating scale at baseline, even though they rated 3 or greater at screening, which explains the lower mean baseline pain scores in Table 1.

Association Between Adherence to MKN and Changes in Pain Across Arms

Pearson Correlations were used to examine the relationship between measures of adherence to MKN (ie, total days in ketosis across 6-weeks, ketones at 3-months post intervention, and self-reported adherence) and changes in pain (ie, pain intensity, pain interference, disability, and PGIC rating) across arms. The results of the correlation analyses are listed in Table 2. Across arms, there was no association between total days in ketosis during the 6-week intervention and changes in pain intensity from baseline to 6-weeks ($r = -0.172$; $p = 0.468$) or changes in pain interference from baseline to 6-weeks ($r = -0.129$; $p = 0.588$). Additionally, there was no association between total days in ketosis across the 6-week intervention and changes in pain-related disability from baseline to 6-weeks ($r = -0.289$; $p = 0.244$). At 3-months post intervention, there was no association between ketone levels and changes in pain interference ($r = 0.168$; $p = 0.519$) or changes in pain intensity ($r = 0.129$; $p = 0.622$). Additionally, there was no association between ketone levels at 3-months

Table 1 Baseline Characteristics by Arm for Participants with Moderate Pain at Screening

Baseline Characteristic	n	MKNA Arm Mean (SD)	n	MKNE Arm Mean (SD)	p-value	Arms Combined Mean (SD)
Female, n (%)	11	9, 81.8%	13	9, 69.2%	0.500	18, 75.0%
Age (years)	11	73.0 (7.4)	13	75.1 (7.3)	0.496	74.13 (7.2)
BPI- Pain intensity score	10	3.48 (1.8)	13	2.35 (1.3)	0.095	2.84 (1.61)
BPI- Pain interference score	10	2.80 (2.6)	13	1.20 (1.2)	0.057	1.90 (2.02)
RMDQ- Disability score	11	6.82 (4.0)	13	6.15 (5.3)	0.737	6.46 (4.68)
RMDQ- Intensity score	10	4.20 (2.8)	13	2.69 (1.5)	0.116	3.35 (2.27)
Glucose (mg/dL)	9	108.9 (20)	11	105.8 (16)	0.706	107.2 (17.4)
Weight (lbs.)	11	165.7 (25)	13	158.5 (36)	0.583	161.8 (31.0)
PHQ-9 total (1–27)	11	3.27 (1.8)	13	2.92 (2.5)	0.703	3.08 (2.20)
PSQI- Sleep quality (1–4)	8	1.88 (0.35)	8	1.88 (0.99)	1.000	1.88 (0.72)

Abbreviations: SD, standard deviations; n, number of participants; BPI, Brief Pain Inventory; RMDQ, Roland-Morris Disability Questionnaire; MKNA, Mediterranean Ketogenic Nutrition Adherence; MKNE, Mediterranean Ketogenic Nutrition Education; PHQ, Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; lbs, pounds.

Table 2 Association Between Adherence to MKN and Changes in Pain for Participants with Moderate Pain at Screening

Independent Variable	Dependent Variable	n	r	p
Total ketones across 6-weeks[a]	Change in BPI intensity	20	−0.172	0.468
Total ketones across 6-weeks[a]	Change in BPI interference	20	−0.129	0.588
Total ketones across 6-weeks[a]	Change in RMDQ score	18	−0.289	0.244
Total ketones across 6 weeks[a]	PGIC rating (6-week)	17	0.473	0.055
Total adherence across 6 weeks	PGIC rating (6-week)	17	0.592	0.012*
3-month ketones	Change in BPI intensity	17	0.129	0.622
3-month ketones	Change in BPI interference	17	0.168	0.519
3-month ketones	Change in RMDQ score	18	0.132	0.601
3-month ketones	PGIC rating (3-month)	17	0.047	0.858
3-month adherence rating	PGIC rating (3-month)	17	0.320	0.211

Notes: [a]Total days above trace level ketones across the 6-weeks. *p< 0.05, two-tailed.
Abbreviations: BPI, Brief Pain Inventory; RMDQ, Roland-Morris Disability Questionnaire; PGIC, Patient's Global Impression of Change; n, sample size; r, Pearson correlation coefficient; p, p-value.

post intervention and changes in disability ($r = 0.132$, $p = 0.601$). The association between total days in ketosis during the intervention and greater improvements in pain on the PGIC scale at 6-weeks approached significance ($r = 0.473$; $p = 0.055$). Additionally, higher levels of total self-reported adherence summed across the 6-week intervention were significantly associated with greater changes in pain on the PGIC scale at 6-weeks ($r = 0.592$; $p = 0.012$). At 3-months post intervention, ketone levels were not associated with improvements in pain on the PGIC rating ($r = 0.047$; $p = 0.858$). Additionally, self-reported adherence was not significantly associated with changes in pain on the PGIC rating at 3-months post intervention ($r = 0.320$; $p = 0.211$).

Changes in Pain Intensity and Pain Interference Between Arms

Paired sample T-tests were used to examine changes in self-reported pain intensity and pain interference in the MKNA arm and MKNE arm. Mean changes in self-reported pain for the pain sample from baseline to 6-weeks are shown in Table 3. From baseline to 6 weeks, 9 participants in the MKNA arm and 11 participants in the MKNE arm were included in the analysis. Changes in mean pain interference were clinically significant for the MKNA arm *(% Change* = −45.2; $d = -0.727$, $p = 0.061$). Changes in mean pain-related disability were also clinically significant for the MKNA arm *(% change* = −35.6%; $d = -0.631$, $p = 0.095$). ANCOVA tests were used to assess differences in changes in pain outcomes from baseline to 6-weeks between arms. The change in pain outcomes from baseline to 6-weeks were used as the dependent variables, arm was used as the fixed effect, and the baseline

Table 3 Mean Changes in Outcomes from Baseline to 6-Weeks Post Intervention by Arm

	Baseline	6-Week	n	Change from Baseline to 6-Week	% Change	Effect Size
MKNA Arm						
BPI Pain intensity (0–10)	3.42 (1.9)	3.31 (2.2)	9	−0.111 (1.4)	−3.22%	−0.080
BPI Pain interference (0–10)	2.90 (2.7)	1.59 (1.7)	9	−1.318 (1.8)	−45.2%	−0.727
RMDQ disability (0–24)	6.89 (3.1)	4.44 (3.2)	9	−2.440 (3.9)	−35.6%	−0.631
RMDQ intensity (0–10)	4.25 (2.4)	3.38 (1.8)	8	−0.875 (2.4)	−20.5%	−0.362
MKNE Arm						
BPI Pain intensity (0–10)	2.32 (1.1)	2.16 (1.2)	11	−0.159 (1.2)	−6.90%	−0.135
BPI Pain interference (0–10)	1.31 (1.2)	1.29 (1.2)	11	−0.026 (1.1)	−1.53%	−0.023
RMDQ disability (0–24)	5.00 (4.9)	4.00 (5.0)	11	−1.000 (1.9)	−25.0%	−0.542
RMDQ intensity (0–10)	2.30 (1.5)	2.20 (1.7)	10	−0.100 (2.1)	−4.35%	−0.047

Note: Standard deviations are in parentheses.
Abbreviations: BPI, Brief Pain Inventory; RMDQ, Roland-Morris Disability Questionnaire; MKNA, Mediterranean Ketogenic Nutrition Adherence; MKNE, Mediterranean Ketogenic Nutrition Education; n, sample size.

outcome score was used as the covariate. When controlling for baseline pain scores, there were no significant differences between changes in pain intensity, pain interference, or pain-related disability from baseline to 6-weeks between arms.

Mean changes in self-reported pain from baseline to 3-months post intervention for the pain sample are shown in Table 4. There were no statistically significant reductions in mean pain intensity from baseline to 3-months post intervention for either arm but approached significance for the MKNE arm ($M = -0.556$, $SD = 0.77$, $p = 0.062$). Reduction in mean pain intensity was clinically significant for the MKNE arm from baseline to 3-months post intervention ($d = -0.723$). Reductions in mean pain interference remained clinically significant for the MKNA arm (*% change*= −43.7.0%, $d = -0.435$, $p = 0.258$) from baseline to 3-months post intervention. Changes in pain-related disability from baseline to 3-months post intervention were not statistically or clinically significant for either arm. ANCOVA tests were used to assess changes in pain outcomes from baseline to 3-months post intervention between arms. When controlling for baseline pain scores, there were no significant differences between arms for changes in pain intensity, pain interference, or pain-related disability from baseline to 3-months post intervention. Note, mean changes in pain for the full sample are reported in Table 5. For the full sample,

Table 4 Mean Changes in Outcomes from Baseline to 3-Months Post Intervention by Arm

	Baseline	3-Month	n	Change from Baseline to 3-Month	% Change	Effect Size
MKNA Arm						
BPI Pain intensity (0–10)	3.34 (2.0)	3.22 (2.2)	8	−0.125 (3.2)	−3.59%	−0.039
BPI Pain interference (0–10)	2.63 (2.7)	1.48 (1.3)	8	−1.149 (2.6)	−43.7%	−0.435
RMDQ (0–24)	7.38 (2.9)	6.25 (4.2)	8	−1.125 (4.7)	−15.3%	−0.239
RMDQ intensity (0–10)	3.78 (2.6)	3.44 (2.5)	9	−0.333 (3.1)	−8.99%	−0.108
MKNE Arm						
BPI Pain intensity (0–10)	2.28 (1.2)	1.72 (1.1)	9	−0.556 (0.77)	−24.6%	−0.723
BPI Pain interference (0–10)	1.37 (1.2)	1.10 (1.0)	9	−0.270 (0.92)	−19.7%	−0.294
RMDQ (0–24)	6.29 (5.8)	7.14 (7.9)	7	+0.857 (2.7)	+13.5%	0.313
RMDQ intensity (0–10)	2.90 (1.5)	2.70 (2.0)	10	−0.200 (2.2)	−6.90%	−0.091

Notes: Standard deviations are in parentheses.
Abbreviations: BPI, Brief Pain Inventory; RMDQ, Roland-Morris Disability Questionnaire; MKNA, Mediterranean Ketogenic Nutrition Adherence; MKNE, Mediterranean Ketogenic Nutrition Education; n, sample size.

Table 5 Mean Changes in Pain Outcomes for All Participants by Arm

	Baseline	6-Week	3-Month	Change from Baseline to 6-Week	% Change (6-Week Minus Baseline)	Change from Baseline to 3-Month	% Change (3-Months Minus Baseline)
MKNA Arm							
BPI intensity	1.67 (1.9)	1.78 (1.9)	1.58 (2.0)	+0.115 (0.96)	+6.59%	−0.048 (1.9)	−3.07%
BPI interference	1.34 (2.1)	0.78 (1.8)	0.70 (1.1)	−0.560 (1.4)	−41.8%	−0.619 (1.7)	−47.0%
RMDQ disability	3.63 (3.8)	2.33 (2.7)	3.00 (4.0)	−1.292 (3.2)	−35.8%	−0.833 (3.3)	−21.7%
RMDQ intensity	2.25 (2.4)	1.83 (1.7)	1.68 (2.1)	−0.417 (1.8)	−18.6%	−0.480 (0.4)	−22.2%
MKNE Arm							
BPI intensity	1.77 (1.2)	1.35 (1.2)	1.20 (1.1)	−0.417 (1.1)	−23.7%	−0.352* (0.70)	−23.1%
BPI interference	0.86 (1.0)	0.74 (1.0)	0.65 (0.79)	−0.124 (0.9)	−14.0%	−0.065 (0.63)	−8.45%
RMDQ disability	3.92 (4.3)	2.28 (3.8)	4.47 (6.3)	−1.640 (3.3)	−41.8%	+0.765 (2.9)	+20.1%
RMDQ intensity	2.18 (1.7)	1.73 (1.4)	2.04 (1.8)	−0.455 (1.9)	−20.6%	−0.435 (1.8)	−17.7%

Notes: Standard deviations are in parentheses. *p< 0.05.
Abbreviations: BPI, Brief Pain Inventory; RMDQ, Roland-Morris Disability Questionnaire; MKNA, Mediterranean Ketogenic Nutrition Adherence; MKNE, Mediterranean Ketogenic Nutrition Education.

participants in the MKNA arm showed clinically significant reductions in pain interference and pain-related disability from baseline to 6-weeks. The results remained clinically significant at 3-months for pain interference. For the full sample MKNE arm, changes in pain-related disability were clinically significant from baseline to 6-weeks but did not remain clinically significant at 3-months post intervention.

Since higher levels of total ketones summed across the 6-week intervention were moderately associated with greater changes in pain on the PGIC scale at 6-weeks ($r = 0.473$; $p = 0.055$), hierarchical linear regression analyses were used to examine this relationship while accounting for other relevant factors such as weight loss, blood glucose, mood, or sleep. Results for the pain sample using the hierarchical multiple linear regression are shown in Table 6. When accounting for

Table 6 Results of Hierarchical Regression Analyses for 6-Week PGIC Rating for Pain Sample

Predictor Variables	B	SEB	β	p	R^2
Weight Loss					
Model 1					0.172
Constant	3.115	0.542	–	<0.001**	
Total Ketones	0.076	0.037	0.473	0.055	
Model 2					0.168
Constant	3.064	0.546	–	<0.001**	
Total Ketones	0.086	0.038	0.533	0.041*	
Change in weight	0.027	0.028	0.227	0.352	
BGL (6-week)					
Model 1					0.258
Constant	2.955	0.595	–	<0.001**	
Total Ketones	0.082	0.040	0.508	0.064	
Model 2					0.262
Constant	3.947	3.946	–	0.339	
Total Ketones	0.087	0.045	0.535	0.082	
BGL (6-week)	−0.010	0.038	−0.071	0.804	

(*Continued*)

Table 6 (Continued).

Predictor Variables	B	SEB	β	p	R^2
PHQ-9 total (6-week)					
Model 1					0.224
Constant	3.115	0.542	–	<0.001**	
Total Ketones	0.076	0.037	0.473	0.055	
Model 2					0.256
Constant	3.605	0.835	–	<0.001**	
Total Ketones	0.064	0.040	0.397	0.136	
PHQ-9 tot (6-week)	−0.156	0.200	−0.195	0.449	
PSQI Sleep Quality (6-week)					
Model 1					0.224
Constant	3.115	0.542	–	<0.001**	
Total Ketones	0.076	0.037	0.473	0.055	
Model 2					0.245
Constant	2.265	1.479	–	0.148	
Total Ketones	0.083	0.039	0.518	0.051	
PSQI (6-week)	0.476	0.767	0.151	0.545	

Notes: *p< 0.05. **p< 0.01. N=24.
Abbreviations: PGIC, Patient's Global Impression of Change; PHQ, Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; BGL, blood glucose level. B, unstandardized slope; SE, standard error; β, standardized slope; R^2, coefficient of determination; p, p-value.

changes in weight and sleep quality as potential covariates, ketone levels remained a predictor of improvements in pain on the PGIC scale at 6-weeks (*ps*<0.055). However, when accounting for blood glucose levels and mood as potential covariates, ketone levels were not a significant predictor of improvements in pain on the PGIC scale at 6-weeks.

Discussion

The primary aim of this study was to determine the effects of an MKN program on self-reported pain in older adults with possible mild cognitive impairment. Given the link between chronic pain and cognitive impairment, it is important to examine the use of nonpharmacological interventions for pain management in older adults.[4] Anti-inflammatory diets such as MKN may promote improvements in pain and have benefits for older adults with mild cognitive impairment.[16] The current study extends prior work in humans and animals by examining the effects of MKN on pain in older adults with possible mild cognitive impairment. Our findings suggest that, although not powered to determine whether the MI-BCT components may promote greater improvements in pain, the use of MKN may provide benefits for pain intensity, pain interference, and patient impression of change that should be intentionally explored in future clinical trials.

First, we examined between group differences (MKNA vs MKNE) in pain interference, pain intensity, and pain-related disability at baseline, 6-weeks, and 3-months post intervention. There were no significant differences in changes in pain over time between the MKNA arm and MKNE arm, but both arms showed clinically meaningful improvements in pain. For the MKNA arm, pain interference showed clinically significant improvement across the 6-week intervention, and this beneficial effect was retained at 3-months post intervention. Additionally, participants in the MKNA arm showed clinically significant reductions in pain-related disability from baseline to 6-weeks, although these effects were washed out by 3-months post intervention. Participants in the MKNE arm also demonstrated clinically significant improvements in pain intensity from baseline to 3-months post intervention. These findings were consistent with previous studies that reported improvements in pain intensity and pain interference in patients who completed ketogenic and other anti-inflammatory dietary interventions.[18,20]

An important consideration when interpreting these between group findings is that the current intervention was not specifically designed to target pain and did not include psychoeducation, MI, or BCT skills that may be relevant and effective in treating pain. For example, cognitive behavioral therapy for pain has strong empirical support for reducing pain and improving quality of life.[46,47] It is plausible that inclusion of psychoeducation and MI-BCT strategies tailored for individuals with chronic pain would produce greater benefits for pain reduction.

The second aim of this study was to assess whether improvements in pain were associated with adherence to MKN across both study arms. Across all participants, urine ketone levels increased during the 6-week program, but ultimately returned to baseline levels at 3-months post intervention as adherence decreased. Higher daily levels of ketones across the 6-week intervention and ketones at 3-months post intervention were not associated with improvements in pain intensity, pain interference, or pain-related disability. The lack of association between ketones and changes in pain interference, pain intensity, or disability may be explained by the small sample size and participant attrition at 6-weeks and 3-months post intervention.

In contrast to urine ketones, higher levels of self-reported adherence to MKN across the 6-week intervention was significantly associated with global perceived benefits and reductions of the impact of pain on daily functioning across both arms. These findings were consistent with a previous randomized trial that found greater improvements in migraine pain reported on the same global impression of change scale for patients who completed a vegan diet intervention.[48] The significant association between higher levels of perceived benefits on pain and higher levels of self-reported adherence indicates that self-reported adherence may better capture improvements from the nutrition intervention, regardless of ketone levels. Specifically, self-reported adherence may better capture adherence to the Mediterranean components of the nutrition program and increased consumption of anti-inflammatory and less processed foods. Future studies should evaluate potential additive beneficial effects of using a ketogenic macronutrient ratio beyond the benefits of a Mediterranean diet.

For the pain sub-sample, the association between adherence to MKN and improvements in pain remained significant even after accounting for the effects of weight loss and sleep quality. In contrast to a pilot study that found reductions in weight to be a confounding variable on improvements in pain for patients who completed a whole-food ketogenic diet intervention, higher ratings on the PGIC were not accounted for by weight loss across arms.[18] That is, even though participants lost weight, global perceived benefits remained significantly associated with higher number of days in ketosis across the intervention. Our finding was consistent with a pilot trial that reported improvements in pain, independent of weight loss for patients who completed a 7-week ketogenic diet intervention.[19] Therefore, improvements in pain may be influenced by anti-inflammatory effects of MKN, rather than the reduction of inflammation from weight loss.[49] Furthermore, previous studies found that ketosis was associated with improvements in sleep quality and mood, which may promote greater improvements in pain.[18,50–52] In contrast to previous studies, sleep quality did not account for improvements in pain on the PGIC scale across arms. The result of this study suggests that improvements in pain from MKN may be independent of sleep quality and weight loss.

Limitations

Several limitations of this study should be acknowledged. First, the pilot control trial had a relatively small sample size overall (N = 58), and both arms had a low number of participants (n = 29). Additionally, fewer participants completed the pain questionnaires at 6-weeks and 3-months post intervention, which reduced the sample size and statistical power. Second, recruitment of participants for the pilot trial did not focus primarily on patients with moderate levels of pain at baseline. At screening, only 24 participants reported pain of 3 or greater (on a scale of 0–10) using the Roland-Morris Pain and Disability Questionnaire. Low baseline levels of pain may have led to a ceiling effect and reduced our ability to detect significant changes. Additionally, ketone levels were measured via home urinalysis testing throughout the intervention and self-reported on a weekly basis, limiting the validity of urine ketone values as they may have been misinterpreted by participants. The active comparator arm may have been too robust of an intervention to show greater differences in pain compared to the MKNE arm.

Next, although the study was designed to reduce potential placebo effects by limiting information about the differences between the two arms at baseline, it is important to acknowledge that placebo could still drive overall changes in self-reported pain. This is particularly the case for aggregate effects evaluated across the two arms. It is possible that simply completing repeated measures of pain and some aspects of the intervention discussions might lead participants to expect improvements in their pain, thereby increasing risk for a placebo response. For example, the association between higher levels of self-reported adherence and pain-related change on the PGIC may be related to expectations that being adherent would improve pain.

However, findings that objective measures of ketosis also related to pain bolster the potential validity of our results. Future studies should use waitlist controls or other pain treatments in order to reduce placebo effects.

Conclusions

Results of this secondary analysis of a pilot MKNA program on reported pain are generally consistent with previous studies finding improvements in pain from KN.[18,20] Although the MKNA program did not promote significantly greater improvements in pain compared to the MKNE arm, both arms showed clinically meaningful improvements in pain after completing the MKN intervention. Additionally, higher levels of self-reported adherence across the 6-week intervention were associated with greater ratings of pain-related change on the PGIC across arms. Future studies should include a larger sample size and focus on recruiting participants with moderate pain at baseline to better assess the effects of MKN on pain in older adults with mild cognitive impairment. Additionally, future studies may utilize MI-CBT strategies and education designed specifically to target pain, in addition to materials focused on MKN and nutrition change. Finally, in order to reduce the potential for placebo effects, future studies should carefully evaluate these effects in comparison to standard treatment and no intervention control groups.

This study assessed the effects of using an MKNA program on reported pain and potential additive benefits of MI-BCT techniques to address pain in older adults with possible mild cognitive impairment. Overall, findings in this pilot clinical trial revealed improvements in reported pain for patients who completed either MKN program arm. The MKNA program did not promote significantly greater improvements in pain compared to the MKNE program. These findings indicate that MKN may be the primary driver of benefits for pain in this intervention. Improvements in pain were associated with adherence to MKN across arms, and exploratory analyses showed that these effects were independent of weight loss, blood glucose, sleep quality, or mood. Our findings demonstrate the potential benefits of MKN on pain and support the need for future full-scale randomized clinical trials evaluating MKN on pain and inflammation in older adults with mild cognitive impairment.

Data Sharing Statement

The individual participant data and study documents that support the findings of this study will not be shared publicly but may be available upon request from the corresponding author.

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Disclosure

The authors declare no conflicts of interest.

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