Pain Medicine, 23(2), 2022, 326–338
doi: 10.1093/pm/pnab278
Advance Access Publication Date: 17 September 2021
Original Research Article

Effects of a Low-Carbohydrate Ketogenic Diet on Reported Pain, Blood Biomarkers and Quality of Life in Patients with Chronic Pain: A Pilot Randomized Clinical Trial

Rowena Field, M. Physio, Fereshteh Pourkazemi, PhD, and Kieron Rooney, PhD

Sydney School of Health Sciences, The University of Sydney, Faculty of Medicine and Health, NSW, Australia

Correspondence to: Kieron Rooney, PhD, The University of Sydney, Faculty of Medicine and Health, Susan Wakil Health Building, NSW, 2006, Sydney, Australia. Tel: +61 2 8627 1877; Fax: +61 2 9351 9204; E-mail: kieron.rooney@sydney.edu.au.

Australian and New Zealand Register of Clinical Trials (ACTRN12620000946910). https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=380106&isReview=true

Date of first enrollment 13/10/20, date of last enrollment 16/12/20

Conflicts of interest: Rowena Field has been supported for the last 2 years by an Australian Government Health Workforce Scholarship Grant issued through the New South Wales Rural Doctors Network to support rural health practitioners' access to postgraduate education. Financial support as a PhD candidate has also been received from The University of Sydney. The co-authors have no conflicts of interests to report.

Received on 30 July 2021; revised on 30 August 2021; Accepted on 14 September 2021

Abstract

Background. A low-carbohydrate ketogenic diet has been reported to improve chronic pain by reducing inflammation, oxidative stress, and sensitivity within the nervous system. The main aim of this trial is to evaluate the effects of a ketogenic diet on reported pain, blood biomarkers and quality of life in patients with chronic pain. **Methods**. Participants with chronic musculoskeletal pain were recruited for a 12-week diet intervention that commenced with a 3-week run-in diet removing ultra-processed foods, followed by randomization to either a whole-food/well-formulated ketogenic diet (WFKD) or to continue with the minimally processed whole-food diet (WFD). Outcome measures included: average pain (visual analogue scale VAS), blood biomarkers, anthropometrics, adherence, depression, anxiety, sleep, ketones, quality of life, diet satisfaction, and macronutrient intake. **Results**. Average weekly pain improved for both groups. WFKD group VAS reduced by 17.9 ± 5.2 mm ($P = .004$) and the WFD group VAS reduced 11.0 ± 9.0 mm ($P = .006$). Both groups also reported improved quality of life (WFKD = 11.5 ± 2.8%, $P = .001$ and WFD = 11.0 ± 3.5%, $P = .014$). The WFKD group also demonstrated significant improvements in pain interference ($P = 0.013$), weight ($P < .005$), depression ($P = .015$), anxiety ($P = .013$), and inflammation (hsCRP) ($P = .009$). Significant average pain reduction remained at three-month follow-up for both groups (WFKD $P = .031$, WFD $P = .011$). **Conclusions**. The implementation of a whole-food diet that restricts ultra-processed foods is a valid pain management tool; however, a low-carbohydrate ketogenic diets may have potentially greater pain reduction, weight loss and mood improvements.

Key Words: Chronic Pain; Randomized Clinical Trial; Ketogenic Diet; Low-Carbohydrate; Nutritional Ketosis; Inflammation; Human; Whole-Food Diet; Quality of Life

Introduction

In Australia, 21% of adults attending general practice present for chronic musculoskeletal pain [1]. Over 31,500 people are referred to pain management services in Australia and New Zealand annually with 40% experiencing pain persisting for over 5 years [2]. While these pain management programs report an overall improvement, there are still many individuals with chronic pain who cannot or choose not to access these services. Other self-management approaches such as modifying lifestyle factors can be beneficial [3].

Among lifestyle factors, change of diet and therapeutic nutrition are becoming recognized as important treatment

options for chronic pain [4–6]. This is supported by recent meta-analyses [4, 7]; however, there is no clear evidence to support a particular type of diet as superior.

A low-carbohydrate ketogenic diet has been used for many chronic metabolic diseases underpinned by meta-flammation (such as diabetes and obesity [8]). The physiological changes that occur in response to carbohydrate restriction (such as lowered blood glucose and reduced insulin requirement) modulates the metabolic dysfunction and produces beneficial therapeutic outcomes. A ketogenic diet has also been reported to improve chronic pain which is frequently comorbid with these diseases [2] and also linked to low-grade systemic inflammation [9]. There are a broad range of physiological changes that occur in response to the diet that also potentially target dysfunction within the nervous system that are implicated in chronic pain.

The restriction of dietary carbohydrate leads to the oxidation of fatty acids and production of ketone bodies in the liver to be used as fuel. As well as an energy source, ketones act as signaling molecules and epigenetic modulators [10], including targets within the nervous system [11]. The overall effect is a decrease in reactive oxygen species [12–14], mitogenesis and mitohormesis [13], stabilization of synaptic functions [15], neurotransmitter optimization [12], decreased inflammation [14], enhanced energy provision [16], and histone deacetylase (HDAC) inhibition promoting epigenetic expression of neuroprotective and neuroplastic factors [17, 18]. Most of the mechanistic research comes from animal models which demonstrate many possible pathways but require caution when translating to the human in its environment [19]. Despite this, human trials point toward a synergistic effect of many pathways restoring homeostatic synaptic function within the nervous system while reducing neuroinflammation and sensitization.

Most human studies reporting neurological outcomes from a ketogenic diet investigate seizure control in epilepsy. These contain both pediatric and adult presentations, controlled trials, uncontrolled trials, retrospective reviews, and case reports [20–22]. Limited trials exists investigating other central nervous system dysfunctions (such as autism, Alzheimer's, and Parkinson's Disease) [23] and psychiatric disorders [24]. The only clinical trial of a low-carbohydrate intervention specifically for musculoskeletal chronic pain identified in a systematic review [4] was for knee osteoarthritis [25]. Overall, the reported outcomes are favorable toward the inclusion of a low-carbohydrate diet in clinical management of nervous system dysfunction.

Our primary hypothesis is that a WFKD will lead to a reduction in reported chronic pain. Sub-hypotheses include: raised ketone levels, improved metabolic health, and improved quality of life will also correlate with reported pain improvements. Furthermore, adequate education and support will lead to a habitual diet with lower levels of carbohydrates. When shifting from a Western style diet to a ketogenic one, it is possible that two variables are altered: diet composition and diet quality. We have included a whole-food run-in diet to allow comparison between these two variables and determine if reducing carbohydrates provides any further benefit. More detail is provided in our published trial protocol [26].

Methods

Study Design

As previously reported in more detail [26], this study was a pilot randomized clinical trial undertaken with ethics approval from The University of Sydney Human Research Ethics Committee (HREC 220/557) and prospectively registered on the Australian and New Zealand Register of Clinical Trials (ACTRN12620000946910).

Procedure

Prior to randomization, a 3-week run-in whole-food diet (WFD) that removed ultra-processed food was implemented. This was followed by random computer-generated assignment to either a whole food/well-formulated ketogenic diet (WFKD) or to continue the run-in diet for a further nine weeks (12 weeks total intervention). Participants were followed up 3 months after the intervention. A study timeline and inclusions are found in Supplementary Data.

Study Population, Recruitment, and Screening

Participants were recruited from the community via local health professionals and social media advertising with contact offered in-person or via telehealth allowing for recruitment across Australia. Recruitment ran from September to December 2020 and follow-up completed by June 2020. Thirty-two potential participants were screened via online questionnaires (Research Electronic Data Capture [REDCap]) for eligibility and 27 enrolled (Figure 1). Participants were included if they were 18 or over, had experienced chronic musculoskeletal pain for over three months, were currently eating a standard western diet, had baseline pain VAS of $\geq$30 mm and agreed to the requirements of the study. Participants were required to maintain their prescribed pain medication but record any changes in optional pain medication use. Participants were eligible for inclusion if they were on medication for metabolic disorders (such as hypertension) if they obtained their doctor's consent to participate and agreed to regular monitoring at a schedule agreed to by their doctor. Applicants were ineligible if they were taking insulin or oral hypoglycemic medications, had a history of eating disorders, bariatric surgery, or recent weight loss. Detailed criteria are listed in the study protocol [26].

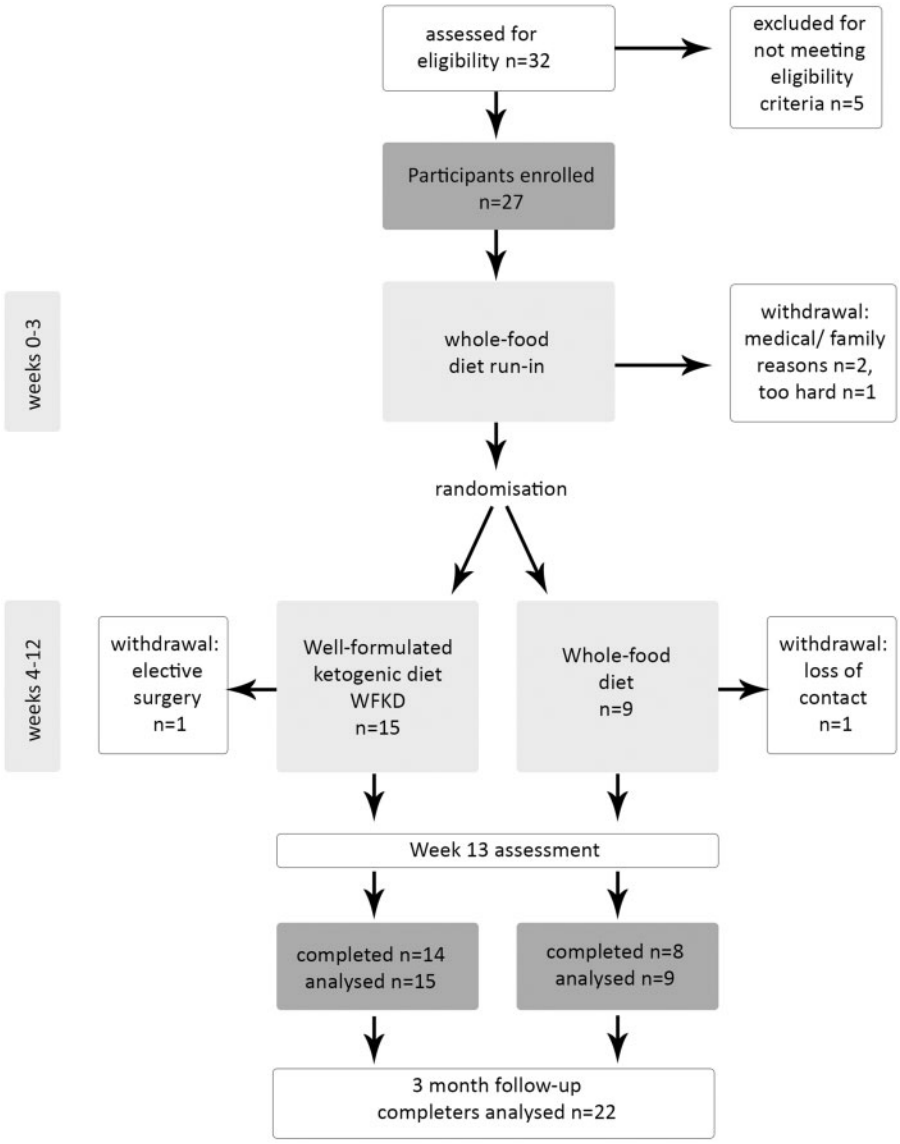


Figure 1. Participant flow through the trial.

Dietary Intervention

The run-in phase involved the removal of ultra-processed foods from the diet based on the NOVA classification system [27, 28] (Supplementary Data) with no emphasis on macronutrient content of the diet. Following randomization in week 3, participants were allocated to continue this diet (WFD) or continue the diet with a reduction in carbohydrate intake to between 30 and 50 g/day to achieve nutritional ketosis with a ketone level of 0.5–3.0 mmol/L (WFKD). Participants monitored ketone levels via finger prick testing using an Abbott Optium Neo blood glucose and ketone monitoring system which meets the standards for in vitro diagnostic test systems (ISO 15197:2013). This allowed for an adaptive approach to titrate carbohydrate up or down to achieve this ketone range. Participants completed an online 24-hour food recall (Automated Self-Administered 24-hour Dietary Assessment Tool [ASA24], Australian version) approximately each fortnight to evaluate dietary intake. Both groups were provided with resources (including handouts with diet guidelines, food lists, and recipes) and fortnightly contact with the researcher (physiotherapist) to assist in dietary change. The WFKD group was also supplied with additional resources developed by the researcher and study dietitian that outlined the top 10 low-carbohydrate food sources for each essential micronutrient to ensure nutrient sufficiency, as well as reputable websites to go to for information (such as dietdoctor.com) and a private study Pinterest page with recipes and informational video links. Participants were provided with Abbott Optium Neo, but were not compensated in any other way and were required to purchase their own food.

Primary Outcome Measures

Pain reduction was measured in two ways. First, the Brief Pain Index (BPI) [29] was conducted at weeks 0, 13, and

follow-up, which rates pain severity (worst, lowest, average, and current VAS) and pain interference (general activity, mood, walking ability, normal work, relationships with others, sleep, and enjoyment of life VAS) in the previous 24 hours. Second, participants kept a daily online diary (REDCap) rating the worst, least, and average pain VAS for the day.

Secondary Outcome Measures

Other measures include: 1) finger-prick testing for ketones and blood glucose using the Abbott Optium Neo completed at weeks 4 to 12 and recorded in the daily diary, 2) laboratory blood biomarkers measured in the morning fasted at weeks 3 and 13 (through iMedical.com.au who subcontract to several different laboratories across Australia to allow participants to get blood tests done locally) to measure high sensitivity C-reactive protein (hsCRP), erythrocyte sedimentation rate (ESR), fasting glucose and insulin (with HOMA-IR for insulin resistance calculated), blood lipids and lipoproteins, 3) anthropometric tests completed by either the researcher or a health professional local to the participant at weeks 0 and 13 (height, weight, waist, and blood pressure), 4) pain medication change (increase or decrease from previous day recorded in daily diary), 5)macronutrient changes assessed online using ASA24 at pre-screen and weeks 3, 6, 8, 10, 12, and follow-up, and online questionnaires (an adapted quality of life QOL based on validated questionnaires [30, 31], adapted dietary satisfaction questionnaire (DSQ) [32], and additional questions at weeks 0 and 13 and follow-up). Mood, sleep, and adherence (VAS) were also recorded in the daily diary. A study timeline is found in Supplementary Data.

Statistical Analysis

Power calculations were based on the minimal clinical important difference for pain change on a 100 mm VAS of 28 ± 21 mm reported for pain populations with higher reported starting pain [33]. A sample size of 18 (n = 9 per group) was required to achieve 80% power, alpha <0.05, and is comparable to other similar trials [25, 34–36], with the aim of 26 participants recruited to allow for dropouts.

Data setup, choice of statistical tests, assumption testing and analysis of results utilized Laerd Statistical guides (https://statistics.laerd.com/ 2015). Statistical analysis was performed in SPSS version 27 (IBM). Difference between groups at baseline was assessed using an independent *t*-test. Some dependent variables were non-normally distributed as assessed by a Shapiro Wilks test, so a Mann-Whitney *U* test was also used to evaluate the differences between group medians at baseline. Two-way mixed analysis of variance (ANOVA) was used to assess the interaction between diet and groups (WFKD and WKD, between-subjects factor) and diet over time (pre-post diet, within-subjects factor). Data not normally distributed were transformed and re-assessed for assumption violation. Raw data are presented in the descriptive analysis (group means and mean differences) and results noted where transformed data has been used for statistical significance analysis (F values). Data analysis was performed both including and excluding outliers to assess any difference in significance. Outcome data are presented as mean ± standard deviation except for mean differences, which are presented as mean ± standard error of the mean. Alpha was set at 0.05. Primary and secondary analysis for the intervention period was performed on all subjects who were randomization (at week 3) using intention-to-treat analysis with missing data imputed by carrying the last observation forward. Follow-up data analysis incorporated only participants who completed the trial. Descriptive data for participants dropping out prior to randomization were used to assess impact of attrition rates on the outcomes.

Results

Twenty-seven participants (23 female, four male) were enrolled into the study between September and December 2020, fulfilling the recruitment criteria. The average age was 53 ± 13 years (range 37–74 years) with a body mass index (BMI) of 29.5 ± 7.0. There was a range of pain presentations with most participants reporting multiple pain sites; however, the most common pain reported was spinal (nine participants) and six reporting a diagnosis of fibromyalgia. Figure 1 outlines the participant flow through the study.

The group sizes were not equal (WFD n = 9 and WFKD n = 15). This was partially due to a family of three being enrolled as a group (for the purpose of blinding to potential changes in the diet) and randomly allocated to the WFKD group based on the male participant allocation. There was no significant difference between the WFKD group and WFD group means or medians at baseline as assessed by t-test and Mann-Whitney *U* test (Table 1). Three dropouts occurred during the run-in prior to randomization (11% attrition) and were included in the baseline analysis only (Table 1). Dropouts during the intervention phase were equal between groups (one in each group, WFKD in week 9 and WFD in week 8, both female), with their last observations brought forward and included in the analysis. No adverse effects were reported.

Adherence was assessed by the percentage of pain diary entries completed (out of seven possible entries each week for 12 weeks). Participants also rated their adherence to the diet for the day in each diary entry on a 100-point VAS. Average diary completion rate ranged from 33.5% to 97.6% with the WFKD average 69.1% ± 22% and WFD 72.4% ± 22%. Average self-rated daily adherence to the diet ranged between 60.5% and 94.5% with an average of 85% ± 8% (WFKD 82% ± 10%, WFD 87% ± 3%) (Supplementary Data).

Table 1. Comparison of participants at baseline and post-randomization to WFKD and WFD groups

	Baseline Mean ± SD	n = 27 Median	Dropouts n = 3 Mean ± SD	WFKD Mean ± SD	n = 15 Median	WFD Mean ± SD	n = 9 Median
n (M/F)	4/23		0/3	3/12		1/8	
Age (years)	53 ± 13	50	55 ± 8	54 ± 15	49	50 ± 12	51
Weight (kg)	81.9 ± 20.7	80	101 ± 45	79.9 ± 14.1	82.5	78.6 ± 19.2	74.2
BMI (kg/m^2)	29.5 ± 7.0	29	37 ± 15	28.4 ± 4.6	28.9	28.9 ± 6.6	29.5
Waist-to-height ratio	0.58 ± 0.08	0.57	0.66 ± 0.13	0.57 ± 0.07	0.56	0.57 ± 0.08	0.60
Average weekly pain (0–100)	56 ± 20	64	75 ± 15	58 ± 20	65	46 ± 19	40
BPI—Pain intensity score (0–100)	44 ± 15	45	55 ± 1.6	46 ± 14	46	36 ± 17	34
BPI—Pain interference score (0–100)	42 ± 24	40	55 ± 35	47 ± 20	44	30 ± 24	31
Pain duration (years)	8.7 ± 9.4	5	13 ± 18.8	10.1 ± 9.2	10	4.9 ± 4.9	5
Depression (0–100, 0 = no depression)	36 ± 31	30	31 ± 33	40 ± 30	50	30 ± 33	10
Anxiety (0–100, 0 = no anxiety)	45 ± 25	50	48 ± 27	45 ± 24	50	44 ± 29	50
QOL score (higher % = higher QOL)	64 ± 13	63	65 ± 13	62 ± 13	59	68 ± 14	75
ASA24 (measured at pre-screening)	n = 27						
Calories	2,346 ± 927	2,163	1,795 ± 902	2,466 ± 1025	2,350	2,316 ± 769	2,163
Fat (g)	104 ± 43	96	82 ± 44	107 ± 47	101	106 ± 37	96
Protein (g)	107 ± 56	103	88 ± 41	108 ± 52	107	113 ± 70	93
Carbohydrate (g)	213 ± 92	190	153 ± 76	223 ± 110	187	213 ± 55	236
DSQ (0–30, lower is more satisfied)	15.6 ± 5.6	15	14 ± 9	16.5 ± 5.4	15	14.6 ± 5.0	14
Blood profile (measured at week 3)	n = 24						
hsCRP (mg/L)	2.41 ± 2.49	1.22		2.66 ± 2.75	1.20	1.99 ± 2.08	1.24
ESR	9.96 ± 8.18	8.00		8.67 ± 7.35	6.00	11.67 ± 9.21	8.00
HbA1c (%)	5.33 ± 0.30	5.30		5.33 ± 0.30	5.30	5.33 ± 0.34	5.30
Fasting insulin (mU/L)	6.98 ± 4.45	6.00		6.75 ± 4.26	6.00	7.36 ± 4.99	7.00
Fasting glucose	4.85 ± 0.52	4.70		4.83 ± 0.53	4.70	4.88 ± 0.53	4.70
Triglycerides (mmol/L)	1.04 ± 0.46	0.90		0.98 ± 0.38	0.90	1.14 ± 0.58	0.90
Trig: HDL ratio	0.70 ± 0.38	0.61		0.67 ± 0.33	0.60	0.76 ± 0.48	0.70
HOMA-IR	1.55 ± 1.12	1.12		1.52 ± 1.15	1.25	1.60 ± 1.14	1.46

ASA24 = Automated Self-Administered 24-Hour Dietary Assessment Tool; BMI = Body Mass Index; BPI = Brief Pain Inventory (worst score in previous 24 hours); DSQ = Dietary Satisfaction Questionnaire; ESR = erythrocyte sedimentation rate; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance (fasting insulin x fasting glucose/22.5); hsCRP = high sensitivity C-reactive protein; LDL = low-density lipoprotein; n = number; QOL = Quality of Life; trig = triglyceride.

Primary Outcomes During the Intervention Period

Changes in pain scores for average weekly pain (week 0, at week 3/end of the run-in period, and week 13) and BPI measures (week 0 and week 13) were assessed using a two-way mixed ANOVA (Table 2). There was no significant two-way interaction between diet and time (group*-time) for average weekly pain or for BPI intensity and BPI interference. The main effect of time showed a statistically significant difference in mean average weekly pain at the three time points ($P = .001$) as did BPI intensity pre-post intervention ($P = .036$) and BPI interference ($P = .005$). The main effect of group was not statistically significant for any pain measure. There was a significant reduction in average weekly pain between week 0 to week 13 for the WFKD group (VAS reduction of 17.9 ± 5.2 mm, $F = 11.81$, $P = .004$) and BPI interference (VAS reduction 15.7 ± 5.5 mm, $F = 8.19$, $P = .013$) but not BPI intensity (VAS reduction 10.75 ± 5.2, $F = 4.283$, $P = .057$). There was also a significant reduction in average weekly pain for the WFD group (VAS reduction 11 mm ± 9.0, $F = 13.36$, $P = .006$), but not in BPI interference (VAS reduction 10 ± 5.1, $F = 3.788$, $P = .087$) or BPI intensity (VAS reduction 5.5 ± 3.5, $F = 2.462$, $P = .155$). Changes in reported average weekly pain over the course of the study dietary intervention are shown in Figure 2. Individual changes in pain assessed over the trial are presented in Supplementary Data. The change in average pain from week 0 to week 13 in the WFKD group ranged from +10.0 mm to −70.0 mm and in the WFD group of −2.0 mm to −25.0 mm. A Pearson's correlation was run on transformed data (reflect and square root) to correct moderately negatively skewed data indicating a significant correlation between diet adherence and change in pain for the WFKD group r (13) = −0.590, $P = .021$, but not for the WFD group r (7) = −0.398, $P = .288$.

Secondary Outcomes during the Intervention Period

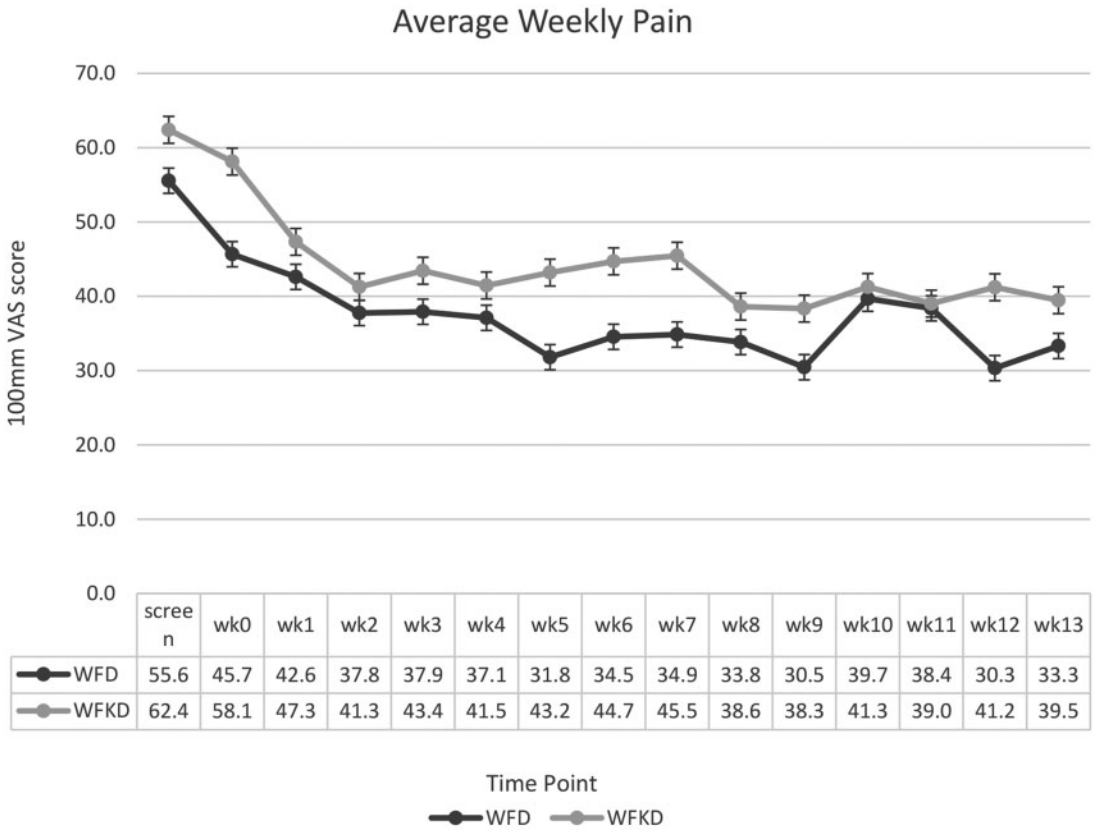
Laboratory blood biomarker analysis showed a significant two-way interaction for hsCRP and diet ($F = 4.57$, $P = .044$), with a significant decrease in hsCRP for the WFKD pre-post diet (−0.32 mg/L ± 0.14, $F = 9.043$, $P = .009$), while WFD group hsCRP increased by 0.33 mg/L ± 0.33. ESR levels did not change significantly for either group but trended upward for the WFD group and approached significance between groups ($P = .057$) (Table 2). No other blood markers showed significant

Table 2. Outcome results for WFKD and WFD groups, n = 24

	WFKD			WFD				
	Week 0 (Mean ± SD)	Week 13 (Mean ± SD)	Mean Change Within Group ◊ (Mean ± SE)	Week 0 (Mean ± SD)	Week 13 (Mean ± SD)	Mean Change Within Group ◊ (Mean ± SE)	Time × Diet (F)§	Mean Between Group Difference At Week 13 ◊ (Mean ± SE)
Weight (kg)	79.9 ± 14.1	76.0 ± 14.0	−3.9 ± 0.6**	78.6 ± 19.2	77.4 ± 18.0	−1.2 ± 0.7	9.047*	1.4 ± 6.6
BMI (kg/m^2)	28.4 ± 4.6	27.0 ± 4.5	−1.4 ± 0.2**	28.9 ± 6.6	28.5 ± 6.3	−0.2 ± 0.1	9.730*	1.5 ± 2.2
WTH ratio	0.57 ± 0.07	0.54 ± 0.07	−0.03 ± 0.01**	0.57 ± 0.08	0.57 ± 0.08	0.00 ± 0.01	5.71*	0.03 ± 0.03
PAIN (0–100 VAS)								
Average weekly	58.1 ± 19.5	40.3 ± 25.0	−17.9 ± 5.2 *	45.7 ± 18.8	34.7 ± 17.6	−11.0 ± 9.0 *	0.702	5.6 ± 9.5
BPI intensity	46.4 ± 13.8	35.7 ± 23.3	−10.75 ± 5.2	36.1 ± 17.2	30.6 ± 13.9	−5.5 ± 3.5	0.521	5.0 ± 8.6
BPI interference	46.9 ± 19.7	31.2 ± 22.8	−15.7 ± 5.5*	29.8 ± 23.5	19.8 ± 18.8	−10.0 ± 5.1	0.490	11.4 ± 9.0
Depression (0–100 VAS)	40.2 ± 29.8	22.9 ± 31.0	−17.3 ± 6.3*	29.7 ± 33.5	26.0 ± 32.7	−3.7 ± 11.8	1.261	3.1 ± 13.3
Anxiety (0–100 VAS)	45 ± 24.4	26.7 ± 28.2	−18.3 ± 6.4 *	44.1 ± 28.8	36.2 ± 33.7	−7.9 ± 13.2	0.630	9.5 ± 12.8
QOL (%, higher better)	61.7 ± 12.6	73.3 ± 11.4	+11.5 ± 2.8**	67.9 ± 14.1	78.8 ± 10.8	+11 ± 3.5*	0.020	5.5 ± 4.7
Mood (0–100 higher better)	57.2 ± 17.3	70.1 ± 19.5	+12.9 ± 3.9*	69.6 ± 10.8	77.6 ± 12.6	+7.9 ± 4.7	0.646	7.4 ± 7.3
Sleep (0–100 higher better)	53.7 ± 16.8	61.3 ± 22.3	+7.7 ± 5.2	63.0 ± 16.0	73.3 ± 16.5	+10.3 ± 7.6	0.089	12.0 ± 8.6
ASA24								
Calories	2466 ± 1025	1664 ± 444	−802 ± 262*	2316 ± 769	1917 ± 430	−399 ± 294	0.970	252 ± 185
Fat (g)	107 ± 47	110 ± 39	+3 ± 12	106 ± 37	93 ± 32	−13 ± 16	0.677	17 ± 15
Protein (g)	108 ± 52	106 ± 35	−2 ± 14	113 ± 70	104 ± 32	−9 ± 15	0.110	2 ± 14
Carbohydrate (g)	223 ± 110	71 ± 41	−153 ± 25**	213 ± 55	156 ± 57	−57 ± 34	5.303*	85 ± 20 **
DSQ (0–30, lower better)	16.5 ± 5.4	14.4 ± 6.0	−2.1 ± 1.4	14.5 ± 5.0	12.8 ± 3.7	−1.8 ± 1.2	0.030	1.6 ± 2.2
Blood profile	Week 3	Week 12		Week 3	Week 12			
hsCRP (mg/L) #	2.66 ± 2.75	2.34 ± 2.54	−0.32 ± 0.14 *	1.99 ± 2.08	2.32 ± 2.32	+0.33 ± 0.33	7.89*	0.02 ± 1.04
ESR mm/hr#	8.7 ± 7.4	7.8 ± 7.7	−0.9 ± 1.0	11.6 ± 9.2	13.4 ± 8.7	+1.8 ± 1.2	2.883	5.6 ± 3.4
HbA1c (%)	5.3 ± 0.3	5.3 ± 0.3	−0.04 ± 0.05	5.3 ± 0.1	5.4 ± 0.4	0.06 ± 0.04	2.362	0.1 ± 0.14
Fasting insulin (mU/L)	6.8 ± 4.3	6.8 ± 4.7	−0.1 ± 0.6	7.4 ± 5.0	7.8 ± 5.3	−0.4 ± 0.7	0.124	0.95 ± 2.1
Fasting glucose	4.8 ± 0.5	4.9 ± 0.5	+0.02 ± 0.1	4.9 ± 0.5	5.0 ± 0.8	+0.1 ± 0.1	0.204	0.12 ± 0.3
Triglycerides (mmol/L)	0.98 ± 0.38	1.00 ± 0.43	+0.02 ± 0.05	1.14 ± 0.58	1.10 ± 0.52	−0.04 ± 0.11	0.320	0.10 ± 0.20
Trig: HDL ratio #	0.67 ± 0.33	0.67 ± 0.35	0.01 ± 0.04	0.76 ± 0.48	0.76 ± 0.44	0.00 ± 0.10	0.014	0.08 ± 0.16
HOMA-IR #	1.51 ± 1.15	1.54 ± 1.26	+0.03 ± 0.15	1.60 ± 1.14	1.74 ± 1.23	+0.13 ± 0.19	0.199	0.20 ± 0.53

ASA24 = Automated Self-Administered 24 hour food recall; BMI = body mass index; BPI = Brief Pain Inventory; DSQ = Diet Satisfaction Questionnaire; HbA1c = glycated hemoglobin; HOMA-IR = homeostatic model assessment of insulin resistance; hsCRP = high sensitivity C-Reactive protein; QOL = Quality of Life questionnaire; SD = standard deviation; SE = standard error; Trig: HDL = triglyceride to high density lipoprotein ratio; WFD = whole food diet; WFKD = well-formulated ketogenic diet; WTH = waist to height ratio.

#Raw data presented in descriptive data, but ANOVA analysis done on square root transformed data for right skewed non-normal distribution and presented as the F value, § two-way mixed analysis of variance (ANOVA), ◊ one-way ANOVA, *P values <.05, **P values <.001.



	screen	wk0	wk1	wk2	wk3	wk4	wk5	wk6	wk7	wk8	wk9	wk10	wk11	wk12	wk13
WFD	55.6	45.7	42.6	37.8	37.9	37.1	31.8	34.5	34.9	33.8	30.5	39.7	38.4	30.3	33.3
WFKD	62.4	58.1	47.3	41.3	43.4	41.5	43.2	44.7	45.5	38.6	38.3	41.3	39.0	41.2	39.5

Figure 2. Average weekly pain scores for WFD and WFKD groups from screening to the end of the dietary intervention.

change. Ketone levels measured via finger prick test and recorded in the pain diary with average ketone levels are shown in Figure 3. There was no significant difference in median ketone levels between groups at week 4 (WFD = 0.0 mmol/L, WKFD = 0.1 mmol/L, $P = .215$) but they were significantly different at 12 weeks (WFD = 0.1 mmol/L, WKFD = 0.25 mmol/L, $P = .005$). At week 12, ketones ranged from 0.0 mmol/L to 0.3 mmol/L in the WFD group and 0.0 mmol/L to 1.1 mmol/L in the WFKD group. There was no significant difference in median ketones between week 4 (0.1 mmol/L) and week 12 (0.1 mmol/L) for the WFD group ($P = .380$), but a significant rise in median ketone level in the WFKD group (0.1 mmol/L to 0.25 mmol/L, $P = .041$) and a significant difference between groups ($P = .005$). There was no correlation for either group between average ketones for weeks 4 to 12 and pain reduction over those weeks.

The Quality of Life (QOL) questionnaire did not show a significant two-way interaction between diet and QOL score ($P = .888$); however, the main effect of time was significant ($P = .000$) with significant improvements for both diet groups between pre- and post-assessment. The WFKD showed an 11.5 ± 2.8% improvement ($F = 16.59$, $P = .001$), and the WFD improved by 11.0 ± 3.5% ($F = 9.893$, $P = .014$). There was a significant improvement in depression VAS for the WFKD group (−17.3 mm ± 6.3, $F = 7.625$, $P = .015$) and anxiety VAS (−18.3 mm ± 6.4, $F = 8.196$, $P = .013$) but not for the WFD group. Other measures of quality of life recorded in the daily in the pain diary included mood and sleep VAS. There was a significant improvement in pre-post mood for the WFKD group (+12.9 mm ± 3.9 points, $P = .005$) but not for the WFD group. There was no significant change in sleep reported.

There was a significant two-way interaction between diet and time for weight ($F = 9.05$, $P = .006$), BMI ($F = 9.73$, $P = .005$) and WTH ratio ($F = 5.71$, $P = .026$), with a significant reduction in average weight pre-post for the WFKD diet (−3.9 kg ± 0.6, $F = 44.45$, $P < .0005$), BMI (−1.4 ± 0.2, $F = 50.64$, $P < .0005$), and WTH ratio (0.03 ± 0.01, $F = 29.5$, $P < .0005$). Individual weight loss ranged from 8.9 kg to 0 kg, with 9/15 reducing their weight by at least 4 kg. There was no significant weight loss for the WFD group (−1.2 ± 0.7 kg), with individual weight loss ranging from −4.4 kg to +2.6 kg. Overall calories were reduced by both groups; however, the WFKD group significantly reduce their energy intake by 802 ± 262 calories ($F = 9.35$, $P = .009$) compared to the WFD who reduced calories by 399 ± 294 calories ($P = .211$).

There was a significant two-way interaction between diet and carbohydrate intake ($F = 5.303$, $P = .031$), with a significant main effect of time ($P = .000$), but the main effect of group not significant. There was a significant difference in carbohydrate intake between groups at the

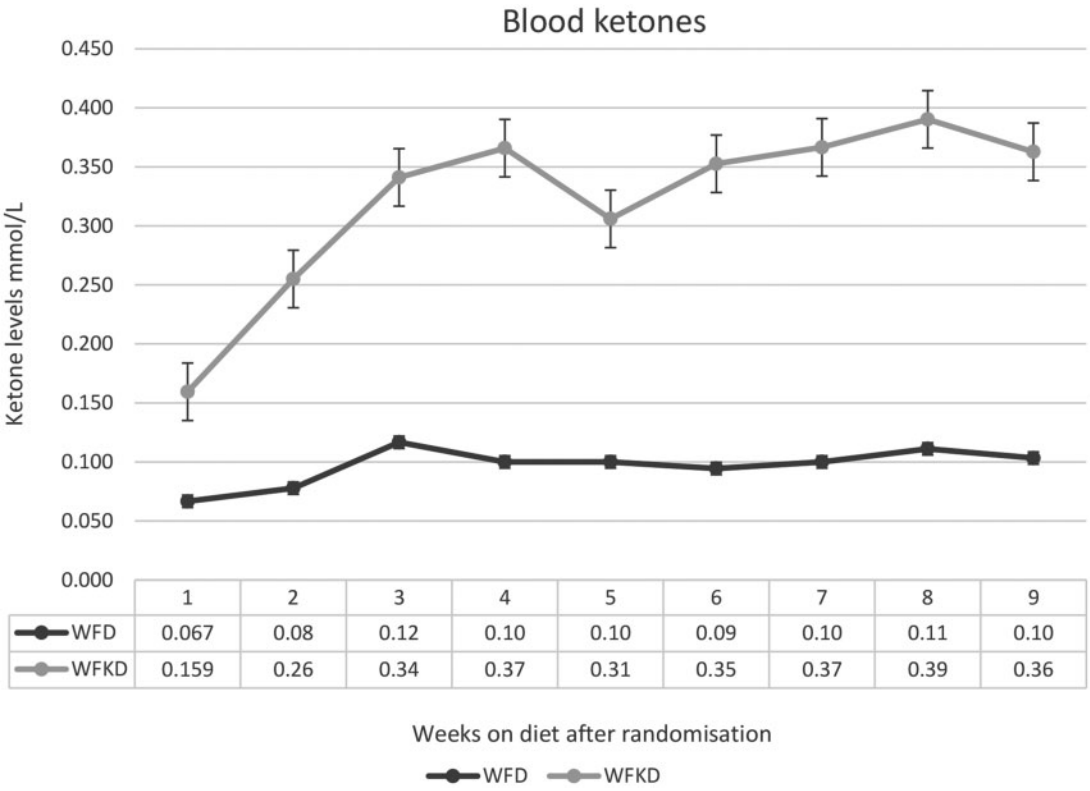


Figure 3. Average weekly ketone scores for WFD and WFKD groups from week 4 to week 12 (9 weeks of the trial post-randomization).

end of the diet intervention (85 g ± 20, $P = .000$), and a significant reduction in carbohydrate by the WFKD group over the intervention (153 g ± 25, $P = .000$) but not the WFD group (−57 g ± 34, $P = .130$). There was no significant change in dietary fat or dietary protein. Changes in macronutrient between pre-screen, week 3, and week 12 are shown in Supplementary Data. There was no significant change in diet satisfaction reported, and both groups rated their success at adhering to the diet as very good (WFKD adherence VAS 80 mm ± 21, range 17–100, WFD adherence VAS 81 mm ± SD 5, range 70–87).

Three-Month Follow-up Outcomes

Twenty-four participants were included in the analysis of the trial period; however, the two dropouts were not included in the 3-month follow-up analysis (18 females, four male, age mean 52.6 years, range 37–74, SD 11.8).

There was no significant two-way interaction between group allocation to the dietary intervention and time for average weekly pain over the intervention and subsequent 3 months. There was a significant main effect of time on average pain over the three time points ($F = 8.356$, $P = .001$), but no significant main effect of group on average pain ($P = .404$) (Table 3). There was no significant difference in average pain between the groups at 3 months. The WFKD group average pain VAS remained significantly reduced by 17.9 mm ± 7.4 at 3 months from baseline levels ($P = 0.031$), and the WFD also remained significantly reduced by 11.4 mm ± 3.3 ($P = 0.01$).

The Brief Pain Inventory (BPI) scores showed a significant main effect for time (BPI intensity $F = 4.266$, $P = .021$, BPI interference $F = 5.025$, $P = .011$), but only the WFKD showed a significant reduction in both scores between baseline and follow-up (BPI intensity VAS −16.6 mm ± 6.0, $P = .016$, BPI interference VAS −16.4 mm ± 6.2, $P = .021$) with the WFD not significant (BPI intensity VAS −4.0 mm ± 5.0, $P = .446$, BPI interference VAS −1.7 mm ± 7.5, $P = .822$).

QOL data had two outliers in the WFKD group at the end of the intervention, and one outlier at 3 months. No other assumptions were violated and analysis with outliers removed did not alter the outcomes. There was no significant two-way interaction between diet and group for quality of life scores, but the main effect of time was significant ($F = 15.760$, $P = <.001$). There was no significant difference in QOL between dietary groups at three months. Both groups showed a significant improvement in QOL between baseline and follow-up, and this improvement was maintained at follow-up. Depression and anxiety VAS were significantly improved for the WFKD between week 0 and week 13 but not between week 0 and follow-up.

There was a significant two-way interaction between group allocation and time for carbohydrate

Table 3. Three-month follow-up outcomes, n = 22

	WFKD				WFD					
	Week 0 (Mean ± SD)	Week 13 (Mean ± SD)	3 Months	3-Month Change Within group ◊ (Mean ± SE)	Week 0 (Mean ± SD)	Week 13 (Mean ± SD)	3 Months	3-Month Change Within group ◊ (Mean ± SE)	Time × Diet (F)§	Mean Between Group Difference at 3 months ◊ (Mean ± SE)
PAIN (0–100 VAS)										
Average weekly	57.7 ± 20.1	38.8 ± 25.3	39.9 ± 29.3	−17.9 ± 7.4*	45.8 ± 20.1	33.4 ± 18.4	34.4 ± 16.7	−11.4 ± 3.3*	0.386	5.5 ± 11.3
BPI intensity	46.4 ± 14.3	34.5 ± 23.7	29.9 ± 25.1	−16.6 ± 6.0*	35.1 ± 18.0	28.9 ± 13.8	31.0 ± 8.3	−4.0 ± 5.0	1.319	1.1 ± 9.2
BPI interference	45.3 ± 19.4	29.1 ± 22.0	28.9 ± 24.8	−16.4 ± 6.2*	29.6 ± 25.1	18.4 ± 19.6	27.9 ± 21.9	−1.7 ± 7.5	1.426	1.01 ± 10.6
Depression (0–100 VAS) #	37.4 ± 28.8	19.7 ± 29.4	25.8 ± 29.2	−11.6 ± 6.7	25.0 ± 32.5	20.9 ± 30.8	27.9 ± 31.2	−2.9 ± 15.8	0.857	2.1 ± 13.3
Anxiety (0–100 VAS)	45.6 ± 25.2	24.3 ± 27.6	39.6 ± 26.9	−6.0 ± 6.5	40.1 ± 28.0	31.3 ± 32.0	44.6 ± 35.6	4.5 ± 10.6	0.593	5.0 ± 13.4
QOL (%, higher better)	63.1 ± 11.8	74.4 ± 2.9	75.6 ± 13.7	12.4 ± 3.5*	66.5 ± 14.4	78.7 ± 11.5	74.6 ± 13.8	8.1 ± 2.2*	0.755	0.94 ± 6.1
ASA24										
Calories	2551 ± 1008	1729 ± 533	1853 ± 715	−698 ± 291*	2320 ± 822	1899 ± 455	1933 ± 683	−388 ± 329	0.586	79 ± 312
Fat (g)	111 ± 46	107 ± 37	98 ± 54	−13 ± 19	107 ± 39	93 ± 34	95 ± 33	−12 ± 13	0.131	3 ± 21
Protein (g)	110 ± 53	103 ± 34	101 ± 45	−9 ± 21	114 ± 75	102 ± 34	90 ± 43	−23 ± 16	0.201	11 ± 20
Carbohydrate (g)	231 ± 109	78 ± 46	115 ± 65	−116 ± 26**	209 ± 58	152 ± 60	162 ± 70	−47 ± 38	3.238*	47 ± 30***

ASA24 = Automated Self-Administered 24 hour food recall; BMI = body mass index; BPI = Brief Pain Inventory; QOL = Quality of Life questionnaire; SD = standard deviation; SE = standard error; WFD = whole food diet; WFKD = well-formulated ketogenic diet.

#Raw data presented in descriptive data but ANOVA analysis done on square root transformed data for right skewed non-normal distribution and presented as the F value/*P* values, § two-way mixed analysis of variance (ANOVA), ◊ one-way ANOVA, **P* values <.05, ***P* values <.001. ***If outlier from WFD group is removed, result is significant (−68 ± 27, *P* = .022). Outlier commenced ketogenic diet after the intervention and was <20 g carb at follow-up.

consumption, but not for the other macronutrients. Carbohydrate consumption in the WFKD remained significantly reduced by 116 g ± 26 ($P = <.001$), whereas the reduction of 47 g ± 38 was not significant for the WFD group ($P = .251$). Based on the allocated diet groups, there was no significant difference between the groups at follow-up. (Supplementary Data). Despite ongoing carbohydrate restriction in the WFKD group, reported habituation of the diet after the 12-week intervention was only fair with 38% saying they continued the diet most of the time (50% for the WFD group). Overall calorie intake for the WFKD also remained significantly reduced at follow up compared to baseline.

Discussion

The primary aim of this 12-week pilot randomized clinical trial was to evaluate changes in chronic pain, demonstrating significant improvements in average weekly pain for both diet groups (Figure 1). The BPI scores for both groups showed improvement but were only significant for BPI interference and approached significance for BPI intensity ($P = .057$) in the WFKD group. This measure is potentially susceptible to daily fluctuations in pain (e.g., the BPI administered on a day where the participant was above or below the weekly average) and given that it was only taken at two time-points, the average weekly pain was a better outcome measure over overall change. Taken together however, the WFKD group experienced greater improvement in pain scores over multiple measures.

The sample size for this study was calculated on a minimum clinically important difference (MCID) of 28 mm ± 21 mm. The mean change in average pain did not reach 28 mm for either group (−17.9 mm for the WFKD group and −11.0 mm for the WFD group), however, five WFKD participants (out of 15) reached the MCID level with a pain score change ≥28 mm, and if the lowest reported in the literature MCID of 8 mm is used [33], 10 out of 15 (66%) had a clinically significant change. For the WFD group, three out of nine (33%) had clinically significant change of ≥28 mm, and eight out of nine (89%) participants did when using the 8 mm MCID. Given the beneficial effect of a whole foods diet for both groups and the flexibility of this approach to fit many dietary styles, this can be recommended for all patients experiencing chronic pain. A ketogenic diet has the potential to gain even further improvements in pain levels and should be offered as an option as part of comprehensive pain management.

Systemic low-grade inflammation (metaflammation) from metabolic imbalance (such as obesity and impaired glucose tolerance) characterizes most lifestyle diseases [37, 38]. Similarly, many chronic pain presentations also exhibit low-grade inflammation [39–42], with metabolic therapies such as dietary intervention a potential treatment strategy [6, 43, 44]. High sensitivity CRP levels reduced for the WFKD by 0.32 mg/L in line with this expectation. However, there was an increase in hsCRP and ESR for the WFD group with a corresponding decrease in pain, suggesting there is more involved than just a reduction in metaflammation.

The ketogenic diet also targets the dysregulation of the glucose-insulin axis that underpins obesity and diabetes [8], with the expectation that a ketogenic diet for pain management could also reduce weight and improve metabolic markers [8]. Participants were not instructed to restrict food or calories during the dietary period, so the weight loss might be explained by increased satiety that is also reported on a ketogenic diet [45]. Both groups reduced calories (WFKD −800 calories, WFD −400 calories); however, only the WFKD reduction was significant. Obesity is frequently comorbid with chronic pain [46], with the participants in this study in the overweight category (WFKD BMI 28.4 ± 4.6, WFD BMI 28.9 ± 6.6). Aside from biomechanical explanations of increased joint loading, another potential driver of pain is the metabolic dysregulation of obesity, which raises metaflammation by triggering the release of inflammatory cytokines from the adipose tissue and articular cartilage [47]. There was a statistically significant weight loss for the WFKD group (4 kg) which may have contributed to the significant reduction in hsCRP and reduced pain levels but unlikely to significantly reduce biomechanical load. The failure of the WFKD to reduce carbohydrate to <50 g/day, and the short term (9 weeks) of the diet may be the reasons for no significant changes in other blood biomarkers, which might have been predicted.

A low-carbohydrate ketogenic diet reduces total carbohydrates to between 20 and 50 g/day producing nutritional ketosis (BOHB of 0.5–3.0 mmol/L) [48]. In this study, neither average carbohydrate restriction nor ketone levels for the WFKD group reached levels that would be considered a low-carbohydrate ketogenic diet even though self-reported adherence to the diet was high (82%). Despite this, there were still significant improvements in pain measures. We must consider then that the improvements in pain reported here may be more related to the removal of ultra-processed foods in conjunction with lowering carbohydrate intake rather than carbohydrate content alone. Blood ketone levels could also be an artefact of the timing of the ketone measurements, with ketone levels measured in the fasted morning state not a true reflection of ketone levels throughout the day. This would be a deviation in the protocol worth considering in follow-up trials to this pilot study. A further reduction in carbohydrates to levels below 50 g/day or an increase in dietary fat may also have produced higher ketone levels and greater changes in pain levels. It is also important to note that the WFD also reduced their carbohydrate intake by 57 g/day when they removed ultra-processed foods from their diet, which are frequently high in processed carbohydrate. The average carbohydrate level at week 13 for the WFD was 156 g, which represents approximately 34% of dietary energy intake, and well below the recommended 45–65% of dietary intake in the

Australian Dietary Guidelines [49], making this a moderate carbohydrate diet [50] and lower in carbohydrate comparative to their starting diet. The reduction in carbohydrates in this group may also help to explain their pain reduction.

Self-rated VAS measures of depression, anxiety, and mood, along with perceived quality of life, all improved significantly on the WFKD diet. Quality of life score also improved in the WFD group without the significant improvement in the other psychological measures. The ketogenic diet has been reported to stabilize mood and provide an antidepressant effect through several mechanisms [51]. These include pathways dealing with cellular energetics and mitochondrial function (improved efficiency as well as alternative energy provision to the brain as ketones when glucose metabolism is dysfunctional), regulation of neurotransmitters and other signaling molecules, as well as reduced levels of oxidative stress and inflammation [51–53]. The outcomes from this study support the potential for a ketogenic diet to improve mood disorders often comorbid with chronic pain.

The strengths of this study design included a run-in phase that reduced the likelihood of dropouts after randomization and the removal of ultra-processed food, which allowed comparison between the WFKD and healthy diet, not a standard western diet. There were also several potential limitations in the current study. First, there was an unequal sample which may have impacted statistical testing. Second, the sample contained a broad range of pain presentations and was mostly female. This may direct future studies to consider a particular pain type, or the influence of the menstrual cycle in a younger female cohort. Third, the ASA24 only calculated the previous 24 hours and may not accurately reflect an average dietary intake. The database is also structured towards a higher carbohydrate diet and did not provide options for lower carbohydrate food options that required corrections (Supplementary Data). Fourthly, lowering carbohydrates also removes foods high in gluten (bread, cakes, and biscuits made on wheat flour) which has been associated with chronic pain presentations [54, 55] and may plausibly alter the pain response for an individual. Fifth, although the ketogenic diet has demonstrated reductions in pain independent of weight reduction, the fact that only the WFKD lost weight may be a confounding factor. Finally, the blood testing was not completed until the end of the run-in period (week 3). As such the participants may all have had some improvement prior to this measurement, potentially decreasing the magnitude of the response and limiting significant findings in blood biomarkers.

Conclusion

This pilot randomized controlled trial demonstrated a significant reduction in reported pain, inflammation, and weight, as well as improved quality of life, depression, anxiety, and mood for participants undertaking a ketogenic diet. In addition, the WFD that eliminated ultra-processed foods also reported pain benefits. Pain reductions were sustained for both dietary groups 3 months after finishing the trial. An appropriate application of these study outcomes for a chronic pain sufferer would be to firstly recommend the removal of ultra-processed foods from the diet followed by offering a WFKD as a targeted metabolic therapy.

Supplementary Data

Supplementary data are available at *Pain Medicine* online.

References

1. González-Chica DA, Vanlint S, Hoon E, Stocks N. Epidemiology of arthritis, chronic back pain, gout, osteoporosis, spondyloarthropathies and rheumatoid arthritis among 1.5 million patients in Australian general practice: NPS MedicineWise MedicineInsight dataset. BMC Musculoskel Dis 2018;19(1):20.
2. Tardif H, Blanchard MB, Quinsey K, et al. Electronic Persistent Pain Outcomes Collaboration Annual Data Report 2018. New South Wales, Australia: Australian Health Services Research Institute; 2019. Available at: https://ro.uow.edu.au/ahsri/1026.
3. Dean E, Soderlund A. What is the role of lifestyle behaviour change associated with non-communicable disease risk in managing musculoskeletal health conditions with special reference to chronic pain? BMC Musculoskelet Disord 2015;16(1):87.
4. Field R, Pourkazemi F, Turton J, Rooney K. Dietary interventions are beneficial for patients with chronic pain: A systematic review with meta-analysis. Pain Med 2021;22(3):694–714.
5. Kaushik AS, Strath LJ, Sorge RE. Dietary interventions for treatment of chronic pain: Oxidative stress and inflammation. Pain Ther 2020;9(2):487–98.
6. Elma Ö, Yilmaz S, Deliens T, et al. Do nutritional factors interact with chronic musculoskeletal pain? A systematic review. J Clin Med 2020;9(3):702.
7. Brain K, Burrows T, Rollo M, et al. A systematic review and meta-analysis of nutrition interventions for chronic noncancer pain. J Hum Nutr Diet 2019;32(2):198–225.
8. Feinman RD. The biochemistry of low-carbohydrate and ketogenic diets. Curr Opin Endocrinol Diabetes Obes 2020;27(5):261–8.
9. Totsch SK, Meir R, Orlandella RM, Norian LA, Sorge R. Effects of diet on immune cells within the central nervous system. Physiol Behav 2018;196(196):158–64.
10. Puchalska P, Crawford PA. Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics. Cell Metab 2017;25(2):262–84.
11. Murano C, Binda A, Palestini P, Baruscotti M, DiFrancesco JC, Rivolta I. Effect of the ketogenic diet in excitable tissues. Am J Physiol-Cell Physiol 2021;320(4):C547–C53.
12. Rho J. How does the ketogenic diet induce anti-seizure effects? Neurosci Lett 2017;637(Supplement C):4–10.
13. Miller V, Villamena F, Volek J. Nutritional ketosis and mitohormesis: Potential implications for mitochondrial function and human health. J Nutr Metab 2018;2018:5157645–27.
14. Pinto A, Bonucci A, Maggi E, Corsi M, Businaro R. Anti-oxidant and anti-inflammatory activity of ketogenic diet: New

perspectives for neuroprotection in Alzheimer's disease. Antioxidants (Basel) 2018;7(5):63.
15. Fedorovich SV, Waseem TV. Metabolic regulation of synaptic activity. Rev Neurosci 2018;29(8):825–35.
16. Cunnane SC, Courchesne-Loyer A, St-Pierre V, et al. Can ketones compensate for deteriorating brain glucose uptake during aging? Implications for the risk and treatment of Alzheimer's disease. Ann N Y Acad Sci 2016;1367(1):12–20.
17. Marosi K, Kim SW, Moehl K, et al. 3-Hydroxybutyrate regulates energy metabolism and induces BDNF expression in cerebral cortical neurons. J Neurochem 2016;139(5):769–81.
18. Wang X, Wu X, Liu Q, et al. Ketogenic metabolism inhibits Histone Deacetylase (HDAC) and reduces oxidative stress after spinal cord injury in rats. Neuroscience 2017;366: 36–43.
19. Field R, Field T, Pourkazemi F, Rooney K. Ketogenic diets and the nervous system: A scoping review of neurological outcomes from nutritional ketosis in animal studies. Nutr Res Rev 2021;1–39 (doi: 10.1017/S0954422421000214).
20. Schoeler NE, Simpson Z, Zhou R, Pujar S, Eltze C, Cross JH. Dietary management of children with super-refractory status epilepticus: A systematic review and experience in a single UK Tertiary Centre. Front Neurol 2021;12:313.
21. Mahmoud S, Ho-Huang E, Buhler J. Systematic review of ketogenic diet use in adult patients with status epilepticus. Epilepsia Open 2020;5(1):10–21.
22. Lyons L, Schoeler NE, Langan D, Cross JH. Use of ketogenic diet therapy in infants with epilepsy: A systematic review and meta-analysis. Epilepsia 2020;61(6):1261–81.
23. Christensen MG, Damsgaard J, Fink-Jensen A. Use of ketogenic diets in the treatment of central nervous system diseases: A systematic review. Nord J Psychiatry 2021;75(1):1–8.
24. Kraeuter A-K, Phillips R, Sarnyai Z. Ketogenic therapy in neurodegenerative and psychiatric disorders: From mice to men. Prog Neuropsychopharmacol Biol Psychiatry 2020;101:109913.
25. Strath L, Lukens S, Jones C, et al. The effect of low-carbohydrate and low-fat diets on pain in individuals with knee osteoarthritis. Pain Med 2020;21(1):150–60.
26. Field R, Pourkazemi F, Rooney K. Effects of a low-carbohydrate ketogenic diet on reported pain, blood biomarkers and quality of life in patients with chronic pain: A pilot randomised clinical trial rationale, study design and protocol. Eur J Integr Med 2021;45:101346.
27. Monteiro CA, Cannon G, Lawrence M, Costa Louzada M, Pereira Machado P. Ultra-Processed Foods, Diet Quality, and Health using the NOVA Classification System. Rome: Food and Agriculture Organization of the United Nations; 2019.
28. Monteiro CA, Cannon G, Moubarac J-C, Levy RB, Louzada MLC, Jaime PC. The UN decade of nutrition, the NOVA food classification and the trouble with ultra-processing. Public Health Nutr 2018;21(1):5–17.
29. Cleeland CS, Ryan KM. Pain assessment: Global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23(2):129–38.
30. Ware JEJ, Kosinski M, Keller SD. A 12-item short-form health survey: Construction of scales and preliminary tests of reliability and validity. Med Care 1996;34(3):220–33.
31. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: Dimensions and practical applications. Health Qual Life Outcomes 2003;1:20.
32. Wolever TM, Chiasson J-L, Josse RG, et al. Effects of changing the amount and source of dietary carbohydrates on symptoms and dietary satisfaction over a 1-year period in subjects with type 2 diabetes: Canadian Trial of Carbohydrates in Diabetes (CCD). Can J Diabetes 2017;41(2):164–76.
33. Olsen MF, Bjerre E, Hansen MD, et al. Pain relief that matters to patients: Systematic review of empirical studies assessing the minimum clinically important difference in acute pain. BMC Med 2017;15(1):35.
34. Zinn C, Schmiedel O, McPhee J, et al. A 12-week, whole-food carbohydrate-restricted feasibility study in overweight children. J Insulin Resist 2018;3(1):1–9.
35. Taylor M, Sullivan D, Mahnken J, Burns J, Swerdlow R. Feasibility and efficacy data from a ketogenic diet intervention in Alzheimer's disease. Alzheimers Dement 2018;4:28–36.
36. Yan N, Xin-Hua W, Lin-Mei Z, et al. Prospective study of the efficacy of a ketogenic diet in 20 patients with Dravet syndrome. Seizure 2018;60:144–8.
37. Gregor M, Hotamisligil G. Inflammatory mechanisms in obesity. Annu Rev Immunol 2011;29(1):415–45.
38. Spite M, Clària J, Serhan C. Resolvins, specialized proresolving lipid mediators, and their potential roles in metabolic diseases. Cell Metab 2014;19(1):21–36.
39. Gerdle B, Bäckryd E, Falkenberg T, Lundström E, Ghafouri B. Changes in inflammatory plasma proteins from patients with chronic pain associated with treatment in an interdisciplinary multimodal rehabilitation program – An explorative multivariate pilot study. Scand J Pain 2019;20(1):125–38.
40. Albrecht D, Ahmed S, Kettner N, et al. Neuroinflammation of the spinal cord and nerve roots in chronic radicular pain patients. Pain 2018;159(5):968–77.
41. Farrell S, de Zoete R, Cabot P, Sterling M. Systemic inflammatory markers in neck pain: A systematic review with meta-analysis. Eur J Pain 2020;24(9):1666–96.
42. van den Berg R, Jongbloed EM, de Schepper EIT, Bierma-Zeinstra SMA, Koes BW, Luijsterburg PAJ. The association between pro-inflammatory biomarkers and nonspecific low back pain: A systematic review. Spine J 2018;18(11): 2140–51.
43. Totsch S, Waite M, Sorge R. Dietary influence on pain via the immune system. In: Theodore JP, Gregory D, eds. Progress in Molecular Biology and Translational Science, vol. 131. Cambridge: Academic Press; 2015: 435–69.
44. Bjørklund G, Aaseth J, Doşa MD, et al. Does diet play a role in reducing nociception related to inflammation and chronic pain? Nutrition 2019;66:153–65.
45. Waldman HS, Krings BM, Smith JW, McAllister MJ. A shift toward a high-fat diet in the current metabolic paradigm: A new perspective. Nutrition 2018;46:33–5.
46. Okifuji A, Hare B. The association between chronic pain and obesity. J Pain Res 2015;8:399–408.
47. Thijssen E, van Caam A, van der Kraan P. Obesity and osteoarthritis, more than just wear and tear: Pivotal roles for inflamed adipose tissue and dyslipidaemia in obesity-induced osteoarthritis. Rheumatology 2015;54(4):588–600.
48. Saslow LR, Kim S, Daubenmier JJ, Moskowitz JT, et al. A randomized pilot trial of a moderate carbohydrate diet compared to a very low carbohydrate diet in overweight or obese individuals with type 2 diabetes mellitus or prediabetes. PLoS One 2014;9 (4):e91027.
49. NHMRC. Australian Dietary Guidelines. Canberra: Department of Health and Aging, National Health and Medical Research Council; 2013.
50. Feinman RD, Pogozelski WK, Astrup A, et al. Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base. Nutrition 2015;31 (1):1–13.
51. Ricci A, Idzikowski MA, Soares CN, Brietzke E. Exploring the mechanisms of action of the antidepressant effect of the ketogenic diet. Rev Neurosci 2020;31(6):637–48.

52. Brietzke E, Mansur RB, Subramaniapillai M, et al. Ketogenic diet as a metabolic therapy for mood disorders: Evidence and developments. Neurosci Biobehav Rev 2018;94:11–6.
53. Morris G, Puri BK, Maes M, Olive L, Berk M, Carvalho AF. The role of microglia in neuroprogressive disorders: Mechanisms and possible neurotherapeutic effects of induced ketosis. Prog Neuropsychopharmacol Biol Psychiatry 2020;99:109858.
54. Isasi C, Stadnitsky A, Casco F, et al. Non-celiac gluten sensitivity and chronic refractory low back pain with spondyloarthritis features. Med Hypotheses 2020;140 :109646.
55. Zis P, Sarrigiannis PG, Rao DG, Hadjivassiliou M. Gluten neuropathy: Prevalence of neuropathic pain and the role of gluten-free diet. J Neurol 2018;265(10):2231–6.