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Effects of differing levels of carbohydrate restriction on mood achievement of nutritional ketosis, and symptoms of carbohydrate withdrawal in healthy adults: A randomized clinical trial

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ABSTRACT

Objectives: To our knowledge, minimal research exists on the effects of diets differing in carbohydrate restriction on symptoms of carbohydrate withdrawal and mood, and the achievement of nutritional ketosis (NK). The aim of this study was to compare ketonaemia, symptoms of carbohydrate withdrawal, and mood. We hypothesized that a moderate carbohydrate restriction would result in fewer symptoms and a reduced effect on mood.
Methods: Seventy-seven healthy participants (25 men and 52 women; mean age: 39 y, range: 25–49; mean body mass index 27 kg/m^2, range: 20–39) were randomized to receive either a very-low-carbohydrate ketogenic diet (VLCKD), low-carbohydrate diet (LCD), or moderately low-carbohydrate diet (MCD), containing 5%, 15%, and 25% total energy (TE) from carbohydrate, respectively, for 3 wk. Fasting blood ketone measures were recorded daily upon waking along with a data from symptom questionnaire and a 5-point mood-state scale. Using analysis of variance and a 5% two-sided α level to determine statistical significance, between-group outcomes were analyzed. Additional association and analyses were conducted by multiple linear regression.
Results: In 75 of 77 initial participants included for analysis, mean serum levels of β-hydroxybutyrate (βOHB) were increased by 0.27 ± 0.32, 0.41 ± 0.38, and 0.62 ± 0.49 mmol/L for MCD, LCD, and VLCKD, respectively (P = 0.013). The achievement of NK was consistent for both VLCKD and LCD groups and sporadic for the MCD group. Only the VLCKD group exhibited 95% confidence interval levels that were consistently ≥0.5 mmol/L. The overall mean change in sum of symptoms scores (SOSS) from baseline was 0.81 ± 2.84 (P < 0.001). Changes in SOSS were highest in the VLCKD group (1.49 ± 2.47), followed by LCD (0.65 ± 2.70) and MCD (0.18 ± 3.3; P = 0.264). Small, statistically significant increases were seen for headache severity, constipation, diarrhea, halitosis, muscle cramps and muscle weakness, and light-headedness, whereas intestinal bloating and craving for sugar and starch improved from baseline. Only halitosis (P = 0.039) and muscle weakness (P = 0.005) differed significantly between the groups. Mood improved significantly from baseline overall, but there was no significant difference between groups (P = 0.181)
Conclusions: Diets containing 5% TE from carbohydrates are ketogenic, but diets containing between 15% and 25% TE from carbohydrates can also result in mean βOHB ≥0.5 mmol/L. There was no meaningful difference in symptoms of carbohydrate withdrawal between diets that contain 5% to 25% TE from carbohydrate, and mood was improved overall, with no significant difference between interventions. Our conclusion, therefore, is that reduced carbohydrate diets should be prescribed by need rather than the desire to mitigate symptoms of carbohydrate withdrawal.

Introduction

Very-low-carbohydrate ketogenic diets (VLCKDs) are beneficial in health conditions ranging from neurologic disorders, cancer, obesity, and diabetes and other metabolic conditions [1–11] and are widely used in the general population for weight loss and weight maintenance [12], and increased satiety [13–15]. Restriction of carbohydrates results in reduced insulin levels and depletes glycogen reserves, which reduces lipogenesis and fat accumulation. Nutritional ketosis (NK) is a natural state stemming from evolutionary adaptations that have allowed humans to survive in the absence of appreciable dietary carbohydrates [16] and is distinct from the pathologic state of ketoacidosis resulting from alcoholism and uncontrolled type

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1 diabetes [17]. These adaptations occurred because the central nervous system, which is typically reliant on glucose as a fuel substrate, requires an alternative fuel during periods of carbohydrate restriction. When glycogen levels become depleted, acetoacetate accumulates and converts to acetone and the preferred fuel ketone body—β-hydroxybutyrate (βOHB)—leading to the presence of ketones in the blood, urine (ketonaemia and ketonuria, respectively), and breath. Ketone bodies are used by most tissue as a source of energy.

Very-low-energy diets and VLCKDs with <50 g/d of total carbohydrates typically result in blood readings of ≥0.5 mmol/L βOHB [18]. This threshold has been used as a cutoff point for entry into ketosis by Guerci et al. [19] and is now applied as a marker for entry into NK in the nutrition field [20,21], as compared with the typically higher levels warranted in the medical field to elicit acute seizure control in children with epilepsy [22].

Many studies have measured the time taken to achieve ketosis, ranging from 1 to 8 d [23–27], but there are inconsistencies in the definitions used for ketosis, and thus, there is a paucity of research that identifies specific time points to NK of ≥0.5 mmol/L βOHB [18–21]. In a previous study comparing a classic ketogenic diet containing 80% total energy (TE) from lipids, to a medium-chain triacylglycerol (MCT)–supplemented diet also containing 80% TE from lipids, we observed the achievement of mean βOHB ≥0.5 mmol/L on day 3 [21]. However, the specific achievement of NK in diets differing in carbohydrate allocation, without the addition of MCTs to modify ketonaemia, has not been evaluated to our knowledge. In one of the few studies comparing a non-ketogenic, low-carbohydrate diet (LCD) with a VLCKD, Johnston et al. recorded mean levels of βOHB at week 2 (of a 6-wk intervention) of 0.7 mmol/L ± 0.2 and 0.2 mmol/L ± 0.0, for the VLCKD and NKLC groups, respectively [28].

Adaptation to a VLCKD, and the achievement of NK, when transitioning from a standard, higher carbohydrate diet, can cause various undesired effects [29]. Symptoms of carbohydrate withdrawal or keto induction are constipation, headache, halitosis, muscle cramps, bloating, diarrhea, general weakness, and rash [30,31]. These occur because of increased urinary sodium, potassium, and water loss during the first 1 to 4 d of a fast or ketogenic diet in response to lowered insulin levels [32–35], and transient reduction in glucose provision to the brain, with blood glucose normalizing after day 4 of the initiation of a VLCKD [36]. These symptoms are often referred to in popular media as “keto flu” but are not well documented in the scientific literature. For example, a Google search returns >22 000 results for the term *keto flu*, but the same term in the scholarly literature returns few results, and to our knowledge, only by the lead authors of the present study [20,21]. Many studies have described adverse effects during ketogenic diets [29–36], but to our knowledge, few studies have specifically described symptoms of keto induction in the short time between commencing a ketogenic diet and the achievement of NK [21,37]. Adverse effects resulting from a VLCKD are likely to reduce the tolerability, and thus, compliance with these diets as clinical interventions [38].

The aim of the present study, therefore, was to investigate, in a randomized clinical trial, the effect of LCDs differing in the magnitude of carbohydrate restriction on symptoms of carbohydrate withdrawal and mood and whether less restrictive LCDs elicit NK of ≥0.5 mmol/L βOHB.

Materials and methods

Population

Seventy-seven participants (25 men, 52 women; mean age: 39 y, range: 25–49; mean body mass index [BMI] 27 kg/m^2, range: 20–39) were recruited between August 7 and 19, 2017 and gave written, informed consent to participate in a 12-wk, randomized, clinical intervention study. The study took place between September 11 and December 10, 2017. Collection of data and analysis was performed at AUT Human Potential Center, Auckland, New Zealand. This study reports results for measures of dietary induction occurring in the first 3 wk of the 12-wk trial. Outcome measures are reported elsewhere [39].

Inclusion and exclusion criteria

Participants were required to be healthy, not seeking weight gain or loss, and between the ages of 25 and 49 y. Exclusion criteria included being underweight (BMI <18.5 kg/m^2), diagnosed with diabetes, diagnosed with any serious medical condition, having previously followed a ketogenic diet, or being a current or former client of any of the researchers in clinical practice.

Ethical approval

The trial was registered by the Australia New Zealand Clinical Trial Registry. Ethical approval for this study was granted by the Southern Committee of the Health and Disability Ethics Committee of New Zealand.

Dietary interventions and allocation

Participants completed baseline testing of blood measures and a lead-in week to identify habitual calorie intake and baseline morning fasted βOHB levels. The study statistician randomized participants, stratified by sex, using a previously prepared sequence, with investigators blinded to treatment allocation. Participants were assigned to the next treatment group according to their order of recruitment. The primary researcher responsible for initial statistical analysis was blinded to the treatment group allocation until the initial analysis was completed. Participants were allocated to one of three LCD plans, a VLCKD, an LCD, and a moderately low-carbohydrate diet (MCD), which advised intakes of 5%, 15%, or 25% TE derived from carbohydrates, respectively.

Diet plans, which included macronutrient and calorie allocation and a sample menu plan, were individualized to each participant, with energy intake determined by the mean reported energy consumed per day in the lead-in dietary recording week. Participants also were provided a workshop to educate them on low-carbohydrate eating, meal planning, and how to use the mobile application and the blood-prick device. Advice was given to limit protein intake to 1.4 g/kg of body mass per day, consistent with the International Society of Sports Nutrition guidelines for optimal protein intake for performance [40]. We chose this as an appropriate protein intake that was not likely to unduly influence the study results because study participants were healthy individuals who also might be engaged in physical activity and sports. Participants were advised to adhere as strictly as possible to the energy and macronutrient prescription for the first 3 wk of the intervention as the present study describes. Comparisons of outcome measures between groups are reported elsewhere. Usual exercise patterns were continued. Dietary intake was recorded by participants in a mobile application (Fat Secret) with the researchers able to obtain real-time entry on a partner mobile application (Fat Secret Pro). Results were monitored for safety and compliance by the primary researcher and research assistants tasked with data monitoring. Compliance to the dietary allocation was monitored daily by a data monitoring team. Where noncompliance to the dietary allocation, especially for carbohydrates, was noticed, the participant was notified and offered support and advice. Figure 1 provides the instructions for the dietary allocations over the 12-wk study course.

Blood ketone and survey measures

Participants were provided with a Freestyle Optium Neo finger-prick ketometer/glucometer (Abbott Industries, Chicago, IL, USA) and were required to use the device to measure and record fasted βOHB daily upon waking. Participants were also instructed to complete a questionnaire including a keto-induction symptoms questionnaire (Symptom-Q) and a simplified 5-point scale indicator of mood state (Fig. 2) developed by the lead author. The Symptom-Q was based on symptoms observed in previous studies of ketogenic diets. One key question was asked (“In the past 24 h to what extent have you experienced the following symptoms?”) for 12 symptoms or effects: headache, constipation, diarrhea, stomach or intestinal pain, intestinal bloating, change in breath odor, muscle cramps, muscle weakness, skin rash, difficulty concentrating, light-headedness, and craving for sugary or starchy foods. This survey has been previously used in a study comparing NK and symptoms and mood in a ketogenic diet including either MCT supplementation or control [21].

Responses were reported on a Likert scale and scored for analysis as 0: *not at all*; 1: *mild*; 2: *moderate*; 3: *severe*; and 4: *intolerable*, providing an overall sum of symptoms scores (SOSS) between 0 and 48 and individual symptoms scores of 0 to 4 for analysis.

Statistical analyses

Effects of the dietary interventions on βOHB and SOSS resulting from the Symptom-Q and Mood-Q were determined by the change in the mean of the various measures from baseline. The significance of these changes between groups was determined by analysis of variance. Statistical significance was taken at the 5%

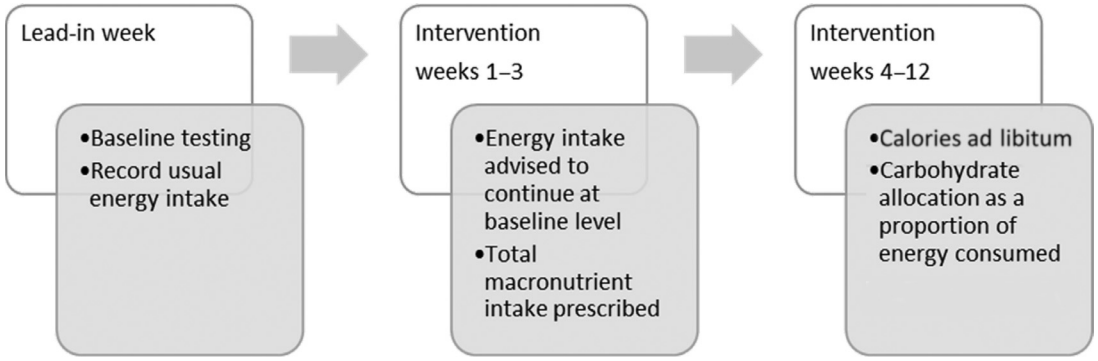

Fig. 1. Instructions for the dietary allocations. Participants were instructed to contact either the registered clinical dietitian or the registered dietitian in the research team for any assistance during the study duration.

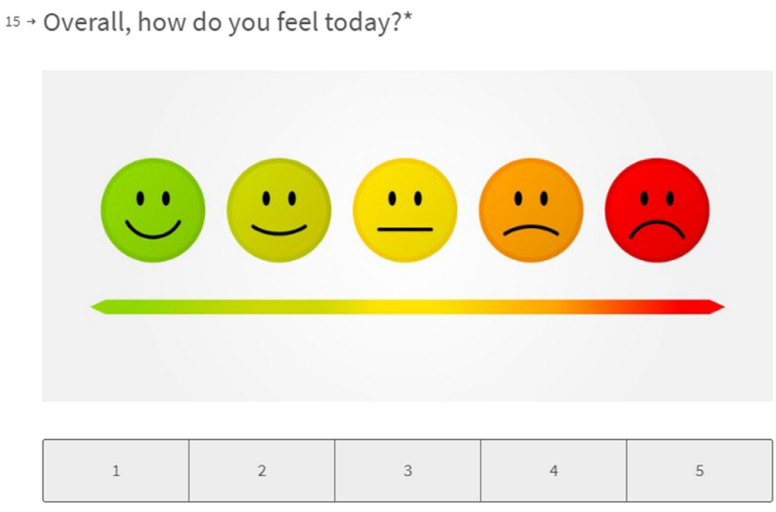

Fig. 2. Five-point mood disturbance scale.

two-sided α level. Further comparisons were made by undertaking multiple linear regression with adjustment made for variables recorded at baseline.

Results

Of 283 individuals assessed for eligibility, 206 were excluded and 77 were included for randomization to the trial groups. The groups did not differ significantly at baseline (Table 1). Two individuals (one man and one woman) failed to comply with guidelines to submit baseline data and withdrew from the study (Fig. 3).

Effects of carbohydrate restriction on βOHB

There was no difference in βOHB between groups at baseline with all groups exhibiting 0.1 mmol/L (95% confidence interval [CI; 0.1−0.1]) in a fasted state on arising. Serum levels of βOHB rose in all groups appreciably with an overall change from baseline of 0.27 ± 0.32, 0.41 ± 0.38, and 0.62 ± 0.49 mmol/L for MCD, LCD, and VLCKD, respectively ($P = 0.013$). All three diets resulted in ketosis with mean levels of βOHB consistent with NK on day 4 for the VLCKD group, and on day 5 for the MCD groups. The mean achievement of NK was maintained post-induction for both VLCKD and LCD groups, except day 20 for LCD, but was more sporadic for the MCD group with NK ≥0.5 mmol/L on day 5. Only the VLCKD group exhibited 95% CI levels that were consistent at ≥0.5 mmol/L, on 14 of 17 d after the achievement of NK, whereas the other groups did not achieve this level of confidence (Fig. 4).

Relatively similar numbers of participants achieved ketosis between the groups, with 78%, 69%, and 85% reaching the threshold for NK at some time during the study period. However, only 9% achieved a mean βOHB consistent with NK in the MCD group, whereas 23% and 46% of participants from the LCD and VLCKD groups, respectively, achieved a mean level ≥0.5 mmol/L βOHB over the course of the study.

Symptoms of carbohydrate withdrawal

The mean SOSS scores differed at baseline and were 3.94 ± 3.84, 2.35 ± 2.78, and 4.36 ± 3.75 for VLCKD, LCD, and MCD, respectively ($P < 0.001$). Mean change in SOSS from baseline overall were 0.81 ± 2.84 ($P < 0.001$). We observed minor changes that were highest in the VLCKD group (1.49 ± 2.47), followed by LCD (0.65 ± 2.70), and MCD (0.18 ± 3.3). Between-group differences did not reach the threshold for statistical significance ($P = 0.264$; Table 2).

There were identical return-to-baseline SOSS scores for VLCKD and LCD on day 18, with the most rapid return to baseline seen in the MCD group on day 11 (Fig. 5). The magnitude of both symptoms of carbohydrate withdrawal and changes from baseline were small overall with the highest recorded value being 24 out of a maximum of 48. The highest mean value was 7.24 for VLCKD on day 4. Proportional changes from baseline were significant ($P < 0.001$). The proportional changes from baseline were similar for VLCKD and LCD, and

Table 1
Baseline characteristics of study participants*

	Treatment group					
	MCD (n = 23)	LCD (n = 26)	VLCKD (n = 28)	Total (N = 77)	Test	*P*-value
Age, y	39.7 (6.1)	38.7 (7.7)	35.4 (7.1)	37.8 (7.2)	ANOVA	0.083
Sex, %					χ^2	0.922
Female	16 (66.7)	17 (65.4)	19 (70.4)	52 (67.5)		
Male	8 (33.3)	9 (34.6)	8 (29.6)	25 (32.5)		
Ethnicity, %					χ^2	0.634
Asian	2 (8.3)	1 (3.9)	1 (3.7)	4 (5.2)		
European	16 (66.7)	20 (76.9)	20 (74.1)	56 (72.7)		
Maori	5 (20.8)	3 (11.5)	6 (22.2)	14 (18.2)		
Indian	0 (0)	1 (3.9)	0 (0)	1 (1.3)		
Other ethnicity	1 (4.2)	0 (0)	0 (0)	1 (1.3)		
Pacific peoples	0 (0)	1 (3.9)	0 (0)	1 (1.3)		
Weight, kg	80 (14.8)	82.92 (20.1)	78.7 (12.9)	80.5 (16.1)	ANOVA	0.628
Height, m	1.72 (0.09)	1.72 (0.09)	1.72 (0.11)	1.72 (0.09)	ANOVA	0.980
BMI, kg/m^2	26.9 (3.06)	27.9 (4.97)	26.5 (3.13)	27.1 (3.83)	ANOVA	0.396

ANOVA, analysis of variance; BMI, body mass index; LCD, low-carbohydrate diet; MCD, moderately low carbohydrate diet; VLCKD, very-low carbohydrate ketogenic diet
*All values shown as mean (SD).

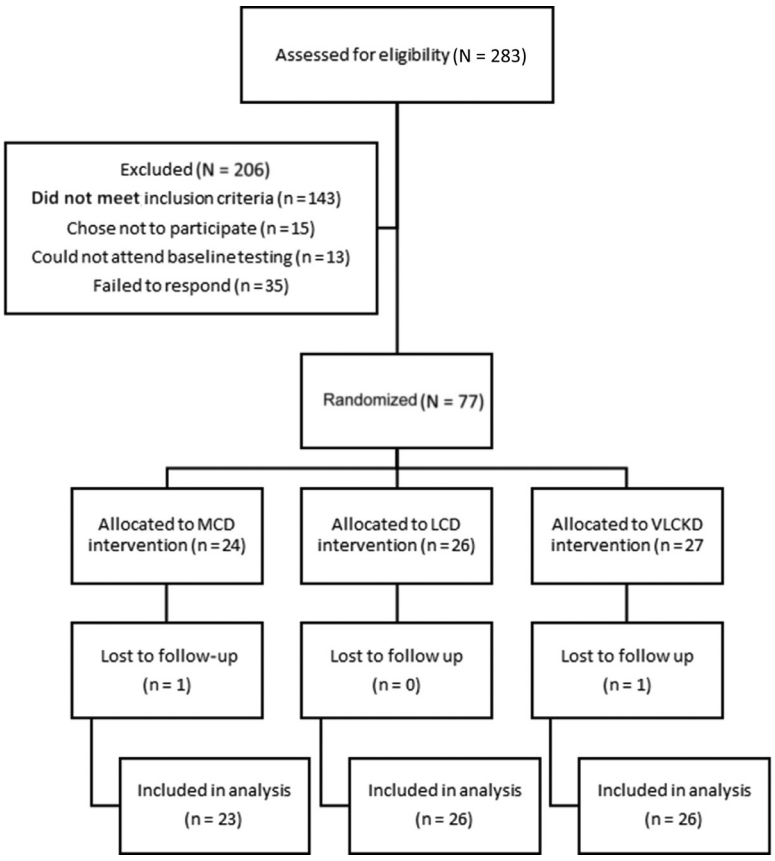

Fig. 3. Participant recruitment, randomization, allocation, and loss to follow-up. LCD, low-carbohydrate diet; MCD, moderately low carbohydrate diet; VLCKD, very-low carbohydrate ketogenic diet.

overall, there was little substantive difference in changes in symptoms between groups (Fig. 5).

Over the 3-wk study period, there was a small, yet statistically significant overall increase in mean headache severity, constipation, diarrhea, halitosis (change in breath odor/"nail polish breath"), muscle cramps and muscle weakness, and light-headedness. Intestinal bloating and craving for sugar and starch improved from baseline. Of these findings, only halitosis (P = 0.039) and muscle weakness (P = 0.005) differed significantly between the groups. Halitosis was highest in the VLCKD group, followed by LCD, and MCD. Muscle weakness worsened most overall in the VLCKD group, followed by MCD, and was least affected by the LCD intervention. All mean changes from baseline for βOHB, symptoms, and mood are presented in Table 2.

Dietary treatment and mood

At baseline, there was a significant difference in mood disturbance scores: MCD 2.37 ± 0.77, LCD 1.84 ± 0.70, and VLCKD 2.11 ± 0.91 (P < 0.001). Consistent improvement in mood (reduced mood disturbance)

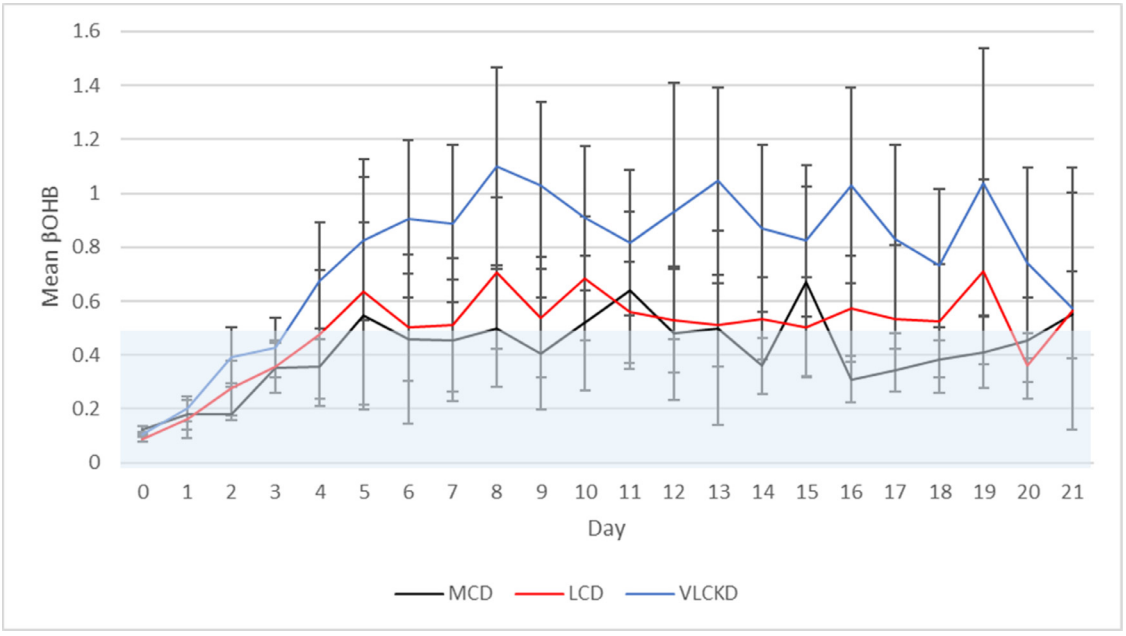

Fig. 4. Mean βOHB by group by day. Bars represent 95% CI. Shaded area represents readings under the threshold for nutritional ketosis. βOHB, β-hydroxybutyrate; LCD, low-carbohydrate diet; MCD, moderately low carbohydrate diet; VLCKD, very-low carbohydrate ketogenic diet.

Table 2
Overall mean and group mean changes from baseline for βOHB, symptom scores, and mood impression

Measure	Overall change Mean change from baseline (95% CI)	Treatment group Mean change from baseline (95% CI)		
		MCD	LCD	VLCKD
βOHB (mmol/L)	0.44 (0.34 to 0.54)	0.27 (0.13 to 0.41)	0.41 (0.26 to 0.57	0.62 (0.42 to 0.82)
P-value	<0.001	0.013		
SOSS	0.81 (0.14 to 1.47)	0.18 (−1.30 to 1.65)	0.65 (−1.17 to 0.33)	1.49 (0.50 to 2.49)
P-value	0.018	0.264		
Headache	0.11 (0.00 to 0.22)	0.12 (−0.09 to 0.32)	0.08 (−4.29 to 1.91)	0.14 (0.01 to 0.28)
P-value	0.042	0.893		
Constipation	0.17 (0.07 to 0.27)	0.12 (−0.10 to 0.34)	0.09 (−0.03 to 0.22)	0.28 (0.09 to 0.47)
P-value	0.002	0.268		
Diarrhea	0.08 (0.00 to 0.15)	0.02 (−0.12 to 0.14)	0.09 (−0.00 to 0.18)	0.11 (−0.05 to 0.27)
P-value	0.040	0.565		
Stomach or intestinal pain	0.04 (−0.05 to 0.14)	0.09 (−0.14 to 0.32)	0.00 (−0.12 to 0.13)	0.04 (−0.13 to 0.21)
P-value	0.364	0.763		
Intestinal bloating	−0.19 (−0.34 to −0.04)	−0.30 (−0.65 to 0.06)	−0.14 (−0.29 to 0.01)	−0.16 (−0.44 to 0.13)
P-value	0.012	0.670		
Change in breath odor/"nail polish breath"	0.29 (0.15 to 0.42)	0.03 (−0.18 to 0.25)	0.36 (0.13 to 0.59)	0.43 (0.19 to 0.67)
P-value	<0.001	0.039		
Muscle cramps	0.09 (0.03 to 0.14)	0.10 (−0.03 to 0.23)	0.01 (−0.07 to 0.09)	0.14 (0.04 to 0.24)
P-value	0.005	0.147		
Muscle weakness	0.33 (0.23 to 43)	0.30 (0.11 to 0.49)	0.14 (0.04 to 0.24)	0.54 (0.32 to 0.75)
P-value	<0.001	0.005		
Skin rash	−0.02 (−0.07 to 0.02)	−0.02 (−0.10 to 0.06)	0.00 (−0.04 to 0.04)	−0.04 (−0.15 to −0.07)
P-value	0.355	0.71		
Difficulty concentrating	−0.02 (−0.14 to 0.11)	−0.04 (−0.26 to 0.19)	0.03 (−0.16 to 0.21)	−0.04 (−0.30 to 0.22)
P-value	0.790	0.889		
Light-headedness	0.21 (0.11 to 0.32)	0.16 (−0.04 to 0.36)	0.16 (−0.04 to 0.37)	0.31 (0.14 to 0.48)
P-value	<0.001	0.419		
Craving for sugary or starchy foods	−0.28 (−0.50 to −0.05)	−0.41 (−0.79 to −0.04)	−0.18 (−0.59 to 0.23)	−0.26 (−0.68 to 0.17)
P-value	0.017	0.708		
Overall mood impression (How do you feel today?)	−0.18 (−0.30 to −0.05)	−0.30 (−0.56 to −0.05)	−0.02 (−0.21 to 0.16)	−0.22 (−0.46 to 0.02)
P-value	0.007	0.181		

βOHB, β-hydroxybutyrate; LCD, low-carbohydrate diet; MCD, moderately low-carbohydrate diet; SOSS, Sum of symptoms score; VLCKD, very-low carbohydrate ketogenic diet.

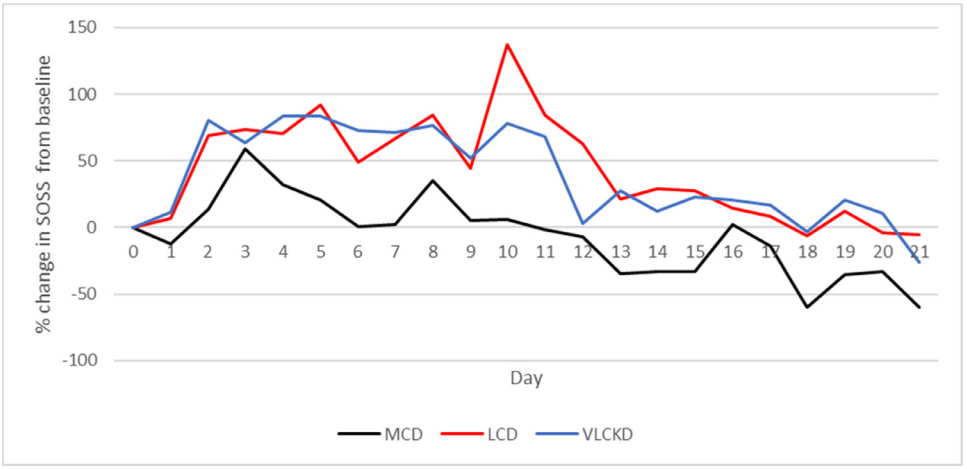

Fig. 5. Percent change in mean SOSS from baseline. LCD, low-carbohydrate diet; MCD, moderately low carbohydrate diet; SOSS, sum of symptom score; VLCKD, very-low carbohydrate ketogenic diet.

was demonstrated for the MCD and VLCKD groups, with mean change from baseline on all days of the study period, whereas the LCD group had some worsening of mean mood scores on 10 of 21 d (Fig. 6). Mood significantly improved from baseline overall, but there was no significant difference between groups ($P = 0.181$; Table 2).

Associations among βOHB, symptoms, and mood

In the present regression analyses, βOHB was not a significant predictor of symptoms of carbohydrate withdrawal (β = 0.019; $P = 0.981$) or overall mood impression (β = 0.107; $P = 0.485$). Of the individual symptoms reported, βOHB was a significant predictor of only muscle weakness (β = 0.300; $P = 0.015$). However, symptoms of carbohydrate withdrawal were a highly significant predictor of mood (β = 0.114; $P < 0.001$).

We performed additional multiple regression analyses to determine any potential associations between baseline cardiometabolic measures and symptoms of carbohydrate withdrawal, and mood disturbance. There were no significant associations between baseline cardiometabolic measures and SOSS or mood disturbance.

Associations between changes in dietary components and mood and symptoms

Mean daily energy intake increased from baseline overall by 87 kcal ± 394 ($P = 0.089$). There was no significant between-group difference for the change in calories from baseline ($P = 0.404$). There was, however, a significant change in mean daily protein from baseline of 24.57 g ± 36.21 ($P < 0.001$). This observed increase in protein did not differ significantly between groups ($P = 0.339$). There were no significant associations between the changes in mean daily carbohydrate, protein, or fat intake, or the change in proportional (%) macronutrient intakes, and SOSS or mood disturbance.

The change in calories from baseline approached the threshold for significance ($P = 0.087$) as a predictor of SOSS (β = −0.002) and was a significant predictor of mood disturbance (β = −0.0004; $P = 0.022$). For every 100-kcal increase in TE, there is a 1% improvement in mood or 0.3% improvement in SOSS. Conversely, reduced mood (i.e., increased mood disturbance score) was a significant predictor of undereating (β = −233.78; $P = 0.022$).

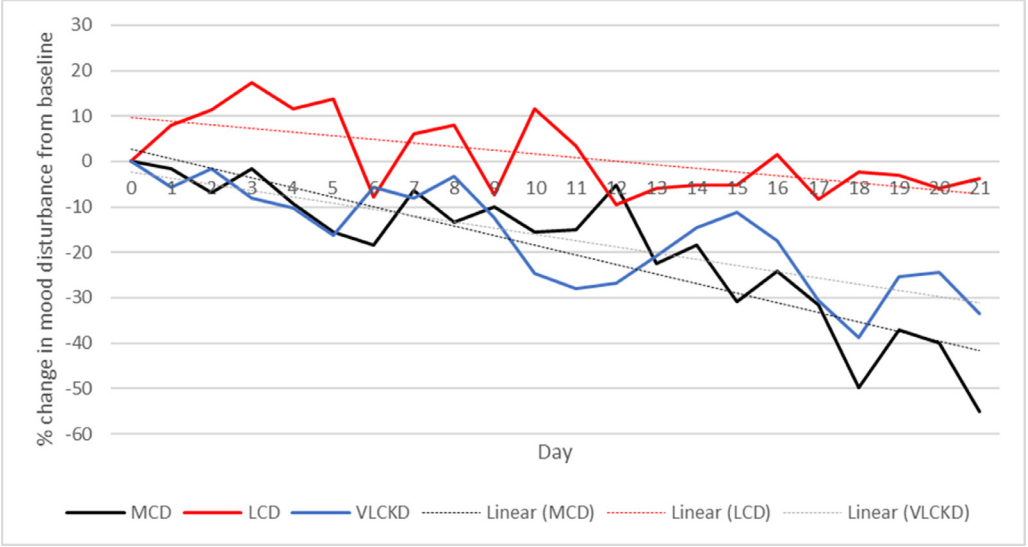

Fig. 6. Percent change in mood disturbance by day, per group. Continuous line shows the mean change from baseline per day; dashed line shows the linear trend. LCD, low-carbohydrate diet; MCD, moderately low carbohydrate diet; VLCKD, very-low carbohydrate ketogenic diet.

Discussion

Principal findings

All diets were functionally ketogenic based on the mean level of βOHB achieved per group but only mean levels of βOHB ≥0.5 mmol/L were demonstrated consistently at levels within the thresholds of 95% CI in the VLCKD group. Ketonaemia is proportionate to the degree of carbohydrate restriction. A 5% carbohydrate allocation is consistently ketogenic for almost all participants, but a low-carbohydrate intervention of 25% or 15% carbohydrate can be ketogenic for some people. Therefore, individuals following less restrictive lower-carbohydrate diets can achieve NK, but this effect is not consistent and to ensure NK there should be a higher lipid-to-non-lipid ratio (i.e., <15% TE derived from carbohydrate).

The adverse effects of carbohydrate withdrawal observed in the literature—headache, constipation, diarrhea, halitosis, muscle cramps and weakness, and light-headedness—were apparent in this study. Although symptoms of carbohydrate withdrawal increased concomitant to the magnitude of carbohydrate restriction, the changes from baseline were small, and there was no significant difference between the intervention groups. Mean reported symptoms differed by <2 out of a possible score of 48 (range between groups: 3.00−4.95), and there is little clinically meaningful difference in adverse effects of carbohydrate withdrawal between diets differing in carbohydrate restriction. Of the symptoms that differed significantly between groups (halitosis and muscle weakness), the difference was also small; <0.4 between groups on a possible 5-point scale. Conversely, intestinal bloating and craving for sugary and starchy foods reduced significantly. There were also non-significant improvements in skin rash and reductions in concentration difficulties. Therefore, the symptoms of carbohydrate withdrawal commonly referred to as keto flu might in actuality mostly result from any appreciable carbohydrate restriction. The keto flu resulting from a VLCKD is limited to the symptoms of breath expression of ketone bodies and a minor increase in muscle weakness. This muscle weakness is likely to be a result of reduced fuel provision while adapting to greater use of fatty acids and ketone bodies for fuel, or owing to the transient natriuresis, kaluresis, and diuresis observed in early keto adaptation [32−35]. Adverse effects need to be weighed against the significant overall improvements in cravings for sugary and starchy foods and reductions in intestinal bloating. Improvements in cravings for sugary foods, in particular, could result in improved compliance to healthier long-term eating behaviors, and reductions in intestinal bloating suggest improvements in digestive function, gut health, or perhaps microbiome status, hypotheses that future research could explore.

Mood improved significantly from baseline as a result of all dietary interventions but did not differ significantly between groups, and the magnitude overall was small. An improvement in mood is a positive outcome, although it is unclear whether these improvements resulted from carbohydrate restriction, increased lipids or protein, or simply from dietary change.

There was a small but potentially meaningful association shown between energy intake and both mood and symptoms of carbohydrate withdrawal suggesting that the magnitude of symptoms experienced with dietary change and disturbance in mood could result from energy restriction rather than the magnitude of carbohydrate restriction.

Strengths and weaknesses of the study

This study was, to our knowledge, the first to specifically assess the effects of diets differing in carbohydrate allocation on the achievement of NK and symptoms of carbohydrate withdrawal and mood. There is a common perception that the adverse effects of carbohydrate withdrawal (sometimes called keto flu in common parlance) are significant barriers to the adoption and maintenance of a VLCD. This was a randomized trial, including food tracking with real-time researcher monitoring and feedback, along with advice and information provided to participants from a competent team with extensive experience in the prescription of LCDs and VLCKDs. As such, we believe it provides a valuable addition to the literature to help inform clinical practice.

The study did not include a control group with a higher carbohydrate allocation consistent with existing dietary guidelines of 45% to 65% of energy derived from carbohydrate [41], as the larger study in which this was embedded was not designed to compare LCDs with usual care protocols.

It is possible that our chosen cohort, who were relatively healthy and absent diagnosed metabolic disorder, may have influenced the results. It is not inconceivable that those who might benefit most from a ketogenic diet might also be those who suffer the worst symptoms of carbohydrate withdrawal and so, further studies in those with metabolic syndrome and diabetes are warranted.

Meanings and implications of the study

This study shows that NK of ≥0.5 mmol/L can be achieved with higher intakes of carbohydrates than are typically prescribed for the achievement of ketosis and some individuals will consistently achieve NK with 15% to 25% TE derived from carbohydrate without the addition of known ketogenic agents such as MCTs. In this study, participants were advised to not consume MCT oil or coconut oil, which contains a high proportion of MCT, as MCTs have been demonstrated consistently to increase ketonaemia and may shorten time to NK [20,21]. However, overall, NK is most effectively achieved by most people, within a lower carbohydrate allocation of 5% TE from carbohydrate.

There are only minor differences in mood and symptoms of carbohydrate withdrawal in healthy individuals from diets differing in carbohydrate allocation ranging from 5% to 25% TE from carbohydrate. Therefore, there appears to be little benefit in a more moderate carbohydrate restriction to reduce symptoms of carbohydrate withdrawal (or keto flu) or reduce mood disturbance when compared with a greater restriction in carbohydrate. Therefore, based on the results of this study, clinicians should prescribe dietary carbohydrate according to need, rather than for the avoidance of adverse effects associated with carbohydrate withdrawal. Conversely, to mitigate the severity of carbohydrate withdrawal symptoms, in the absence of a defined clinical need for the patient to achieve ketosis, a more moderate carbohydrate restriction might be warranted.

Unanswered questions and directions for future research

It is unclear whether these results apply to individuals with metabolic disorders, and thus warrants research to determine the effect of differing dietary allocation of carbohydrate on symptoms of carbohydrate withdrawal and mood for this population. Additional research with larger samples is also warranted to investigate the conclusions of this study further.

Conclusion

Diets differing in carbohydrate allocation between 5% and 25% TE from carbohydrate can be ketogenic and result in mean βOHB ≥0.5 mmol/L. However, this effect varies widely among individuals, and there is a clear effect on ketonaemia and ketosis with greater

carbohydrate restriction. The only diet in this study that was consistently ketogenic was the VLCKD consisting of a carbohydrate allocation of 5% TE from carbohydrate. Symptoms of carbohydrate withdrawal increase with greater carbohydrate restriction, but this increase is small, and there is no meaningful difference between LCDs that contain 5% to 15% TE from carbohydrate, and a more MCD containing 25% TE from carbohydrate. Mood was similarly improved in all interventions by a small magnitude, with no significant difference between interventions. A demonstrated association between reduced energy intake and mood disturbance, which also approached the threshold for significance for symptoms of carbohydrate withdrawal, suggests that calorie sufficiency might be a better mitigator of mood disturbance and adverse effects of dietary change than carbohydrate restriction.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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