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Potential benefits of a ketogenic diet to improve response and recovery from physical exertion in people with Myalgic encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): A feasibility study

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Abstract

Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) affects approximately 250,000 people in the UK. The condition varies in severity causing long-term physical and cognitive fatigue which is not alleviated by rest. Whilst the pathology is not understood, recent evidence suggests metabolic abnormalities may be associated with the manifestation of symptoms, particularly involving the metabolism of glucose and energy production. The use of ketone bodies as an alternative energy substrate may be beneficial to people with ME/CFS, in order to by-pass the glycolytic pathway, enhance energy production and reduce fatiguing outcomes. **Study Design and Methods:** Using a pragmatic collective case study with repeated measures methodology we investigated the feasibility of following a ketogenic diet and potential effects of the high fat, low carbohydrate diet on response to physical activity in people with ME/CFS (n=3) and healthy controls (n=3) using a submaximal exercise stress test both with and without dietary intervention. Exercise tolerance (mins), rate of oxygen consumption (VO_2) to workload (75W), respiratory exchange ratio (RER), rate of perceived effort (RPE) and lactate response were measured throughout and descriptive statistics performed. **Results:** We found that the ketogenic diet was followed, with compliance higher in the pwME/CFS. Variations in response following the ketogenic diet was observed across individuals in minutes performed, VO_2, HR, RER, and RPE post diet but the KD only limited exercise capacity in the control individuals. Individuals responded differently to the KD but group trends have been reported as means and standard deviation. The KD resulted in a decrease in RER at submax in the controls with a mean change of 0.07 from baseline (0.86 ± 0.1) to post intervention (0.79 ± 0.1) compared to a mean change of 0.02 in the ME/CFS from baseline (1.03 ± 0.1) to post intervention (1.01 ± 0.1). A decrease in VO_2 (L/min) at submax showed a mean change of 0.06 (L/min) in the pwME/CFS at baseline (1.34 ± 0.1) to post intervention (1.27 ± 0.2) compared to a mean change of 0.07 (L/min) in the controls at baseline (1.40 ± 0.3) to post intervention (1.33 ± 0.2). HR (bpm) at submax decreased in all individuals, with a mean change of 4 (bpm), with pwME/CFS at baseline (139 ± 8.2) to post intervention (135 ± 14) and control individuals at baseline (107 ± 7.8) to intervention (103 ± 3.2). RPE at submax decreased in the pwME/CFS from baseline (6 ± 1.0) to post intervention (5 ± 2.1) whereas the controls increased from baseline (2 ± 1.0) to post intervention (3 ± 1.5). **Conclusion:** Our observations suggest individualised but metabolic flexibility in healthy individuals is achievable via dietary manipulation showing the ability to switch from glucose to fats under controlled conditions. The different response in substrate utilisation in individuals with ME/CFS suggests that potential metabolic abnormalities may be present in ME/CFS. Further investigation is now warranted in order to assess whether the KD is beneficial for people with ME/CFS.

Keywords: Myalgic Encephalomyelitis, Chronic Fatigue Syndrome, Ketogenic Diet, Diet, Energy Metabolism, Fatigue.

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INTRODUCTION

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic neurological health condition that affects approximately 250,000 people in the UK. It varies in severity, severely impacting on the life quality. Symptoms include long-term debilitating fatigue often accompanied by neurocognitive memory and concentration impairment; post-exertional malaise (PEM) particularly after physical or mental exertion; muscular and joint pain, unrefreshing sleep, flu-like symptoms with tender lymph nodes and sore throat [1]. It has a profound impact on the ability to carry out both physical and cognitive activities of

daily living and is not alleviated by rest [2].

Whilst the pathology is not completely understood, emerging evidence indicates people with ME/CFS (pwME/CFS) have bio-energetic impairments which may be related to mitochondrial dysfunction (MD) and abnormal substrate metabolism which may associate with the manifestation of symptoms [3, 4]. Individuals with ME/CFS show both altered energy metabolism during and recovering from physical activity. Previous studies have shown pwME/CFS to show reduced functional capacity compared to healthy controls during a single VO_{2max} test, with reduced time to anaerobic threshold, VO_2 peak and workload [5-7] with the suggestion that lactate production starts earlier than in healthy controls, reducing maximal exercise capacity [8]. Furthermore, Nicolson and Ellithorpe [9] previously suggested that pwME/CFS may have an increased susceptibility to cellular oxidative stress, resulting in the loss of electron transport chain function due to the accumulation of reactive oxygen species. Under these conditions, glycolysis would increase and result in abnormal lactate production and cellular damage. Limited net energy available to cells may therefore result in anaerobic metabolism. This was later supported by Booth *et al.* [10] who also suggested that this possible compensatory glycolysis mechanism in pwME/CFS results in the need for additional ATP in order to convert lactate back to pyruvate. They suggested that a consequently longer lactate clearance period and the use of additional ATP for this process was unfavourable to such a fatiguing condition and may indeed be responsible for an increase in symptoms.

Importantly, Campagnolo *et al*'s 2017 [11] systematic review found pwME/CFS had an interest in modified diets and supplementation as a way to alleviate symptoms, but existing evidence was found to be insufficient and lacking as a basis for therapeutic treatment in this population group. However, these studies were based on fatigue as the primary outcome measured via questionnaires and non-physiological biomarkers, the reliance on these methods for measuring fatigue can be problematic and often difficult due to subjectivity with differences in both cognitive and physical fatigue. Furthermore, they did not explore bioenergetics or the impact of the KD.

To date, no research has examined the responses to and recovery from a physical activity stressor in pwME/CFS compared to controls on a KD, nor looked at the feasibility of performing such a trial.

The aim of this foundation study was to assess whether the use of ketones as an alternative energy substrate have potential to benefit pwME/CFS? This was achieved through the following objectives: to evaluate the 1) feasibility of a KD intervention in terms of adherence; 2) potential benefits or harms to pwME/CFS on performance during and recovery from an exercise stress; 3) underpinning mechanism for the KD through change in the substrate utilisation

MATERIALS AND METHODS

Study Design

The study was a pragmatic collective case study with a repeated measures methodology that lasted for a total of three weeks, with two testing visits separated by a one-week self-guided dietary intervention. The study was approved by the University Research Ethics Committee, reference: 171125.

Setting

Assessments were carried out by trained researchers in a University setting.

Participants

Participants were recruited from the Oxfordshire area via posters displayed on University notice boards, online social media posts (Twitter) and local ME/CFS support groups. People with a self-reported clinical diagnosis of ME/CFS were screened using the Canadian Consensus Criteria [2] to confirm diagnosis. The control group was a selected convenience sample who showed willingness to participate. Further inclusion criteria for both groups included no significant current or previous medical history or medical conditions/ complications that would preclude safe participation in exercise; no other condition affecting the central nervous system other than ME/CFS; no known conditions that may be associated with fatigue e.g. anaemia; not pregnant; not clinically depressed/ on medication for depression. In addition, willingness to adhere to the ketogenic diet was also discussed and advice on how to adapt their habitual diet was given by a Registered Nutritionist.

For each visit, the participants were asked to fast overnight (approximately 6-8 hours), however they were allowed to drink water. Testing sessions took place before 10:00 am and early as feasibly possible allowing for flexibility and preference for each participant.

Order of events

Visit 1 (Baseline)

On visit one; participants gave written formal consent according to the guidelines laid down in the Declaration of Helsinki.

Following the ACSM guidelines on safe exercise testing [12] all participants were provided with a Physical Activity Readiness Questionnaire (PAR-Q), and an electrocardiogram (ECG) was undertaken to ensure no cardiac abnormalities would prevent them from safely carrying out the exercise test. Any abnormalities would have excluded participants from the study at this point.

Questionnaires were administered to collect basic health information and participant demographics. The Fatigue Severity Scale (FSS) was used in order to assess fatigue levels. The International Physical Activity Questionnaire short form (IPAQ-SF) was used to evaluate participant activity levels over the past 7 days. A trained Nutritionist took a 24-hour diet recall to collect information on what the participants had eaten on the previous day.

Physical baseline measures were recorded, including height (m), weight (kg), heart rate (bpm) and blood pressure (BP).

Exercise stress response and recovery

The protocol performed followed that of Mavrommati *et al*. [13] with the work load starting at 10W. In addition, at the end of each 2-minute step capillary blood was taken via finger prick for glucose (Precision Glucometer) and lactate (Lactate Pro 2, Arkray) levels. In view of the broad range of physical impairment and individual fitness levels in the ME/CFS group, a set end-point based on meeting maximal criteria was not suitable. Therefore, testing was terminated when participants reached volitional exhaustion or if their cadence dropped by 10 RPM. On ceasing exercise, participants were asked their reason for stopping and were encouraged to continue to cycle with no resistance for 1 minute until their HR had recovered back to baseline. During recovery participants were assisted to a chair positioned within 1 meter of the cycle ergometer. Continuous lactate, glucose and blood pressure were recorded along with rate of perceived effort (RPE) until they reached pretest levels.

Safety

Each visit lasted around 2 hours to allow for all measures to be taken, however due to variation in recovery time this was flexible to ensure the participants were fully recovered and felt able to leave. Once recovered they, were provided with a snack and transportation home if

required. Participants were contacted that evening and the next morning to ensure they were not experiencing any adverse effects.

Dietary intervention

Following testing on visit 1, participant blood ketone levels were checked via finger prick using a blood ketone meter (On Call GK Dual, ACON) with expectation that ketone levels were low or 0 mmol/L. Participants were then asked to follow a KD for one week consisting of ~70% fat, ~20% protein and ~10% carbohydrate or <50g of carbohydrates a day in order to put them into light nutritional ketosis (≥0.5mmol/L). The participants were supplied with ketone urinalysis strips (Ketostix, Bayer) and were advised to track their ketone levels from day three of the diet (AM and PM) to assess whether they were complying with the diet. They were also informed that they could contact the Registered Nutritionist if they required further dietary advice.

Due to the possibility of PEM and increased symptoms in the ME/CFS group after the exercise test on visit one, a one week wash out period was undertaken to allow for sufficient recovery time before commencing the KD intervention. If participants required longer, allowances were made to ensure participant wellbeing and to ensure retention.

Visit 2 (Post Ketogenic Diet)

Visit 2 took place after one week of being on the KD. Blood ketone levels were checked to assess whether the participants were in a state of nutritional ketosis suggested by levels of ≥0.5mmol/L. The repeated test was undertaken with the same measures being recorded for comparison. Additionally, post exercise ketone levels were also recorded to assess whether ketones had been utilised throughout the exercise. At the end of the testing session, a Process Evaluation questionnaire was administered to determine acceptability of the intervention including the ease of adherence to the KD and whether there were any perceived benefits.

RESULTS

Descriptive statistics were used to compare demographic characteristics between groups (Table 1).

Table 1: Baseline participant demographic comparison between groups

	ME/CFS group	**Control group**
	(n=3)	**(n=3)**
Gender	Male: 1/ Female: 2	Male: 2/ Female: 1
Age	30 ± 6.8 (25-38)	39 ± 11.5 (28-51)
Weight (kg)	67.8 ± 11 (58-80)	84 ± 13.7 (69-95)
BMI (kg/m^2)	22.3 ± 0.5 (22.1-22.9)	26 ± 4.35 (21.7-28.7)
V'O2/kg max (ml/min/kg)	29.6 ± 4.9	37.3 ± 8.2
FSS	5.6 ± 1	1.6 ± 0.7
IPAQ-SF	Moderate	High
Special Diet	1/3	0/3
Dietary Supplements	3/3	0/3

Values are expressed as means ± standard deviations, or total number of people within each group. IPAQ-SF is categorised by level of activity. BMI: Body Mass Index, VO_{2max}: maximal oxygen uptake, FSS: Fatigue Severity Scale, IPAQ-SF: International Physical Activity Questionnaire-Short Form

Three ME/CFS participants and three non-ME/CFS controls took part in the study. The mean age of the pwME/CFS was 30 (± 6.8) years old in comparison to the controls at 39 (± 11.5) years old. Two out of three (66%) ME/CFS were female compared to one out of three (33%) of the controls. The pwME/CFS were in the healthy BMI range 22.3 (± 0.5) whilst the controls had a mean value of 26 (± 4.35) putting them collectively in the overweight category for BMI (>25) [14]. Observationally it is assumed the participants who were considered in the overweight category for BMI were considered to have a high fat free mass and low body fat percentage. However, anthropometric measures for body composition were not validated upon data collection. Mean measures for the Fatigue Severity Scale showed the pwME/CFS had a fatigue score of 5.6 (± 1) indicating they suffered with fatigue (>4) whereas the controls had a mean score of 1.6 (± 0.7) indicating no or very little fatigue [15]. One out of three of the pwME/CFS was on a modified Paleolithic diet, limiting dairy and grains. All three of the pwME/CFS reported to be taking dietary supplements showing they had an interest in dietary modifications in an attempt to improve their condition.

Individual Dietary Intakes

The 24hr dietary recalls for both the pre and post dietary intervention were analysed using Nutritics© software [16] to assess dietary intake (total energy, carbohydrate, protein and fat) and to evaluate compliance / feasibility to the KD (Table 2).

Table 2: Baseline and post KD measures of macronutrient intake and ketone level

		Energy (kcal)	**Carbohydrate (g)**	**Protein (g)**	**Fat (g)**	**Ketones (mmol/L)**
CFS1	Baseline	1345	125	58	69	0
	Post KD	1464	22	93	108	1
CFS2	Baseline	1472	171	63	60	0
	Post KD	1570	32	92	119	1.2
CFS3	Baseline	2685	227	149	130	0
	Post KD	3055	42	136	260	0.4

Control 1	Baseline	-	-	-	-	0
	Post KD	-	-	-	-	0.5
Control 2	Baseline	1739	204	74	67	0
	Post KD	1097	105	54	50	0.5
Control 3	Baseline	6071	590	301	276	0.2
	Post KD	2871	49	157	220	0.3

Kcal: kilocalories, g: grams, mmol/L: millimoles per litre, '-'denotes missing data

The cardio-pulmonary responses for VO_2, VCO_2, RER and HR were analysed using Metasoft Studio (Cortex) software with individual responses assessed at a fixed workload of 75 watts to allow for a non-discriminatory comparison at the same time point (Table 3). Due to inter-individual variation in performance time, this enabled a direct comparison of output that disregards possible limited exercise capacity in the pwME/CFS [5].

Table 3: Group response to exercise stressor at work intensity of 75 watts

	Visit 1 Baseline		**Visit 2 Post KD**	
	75W		**75W**	
	ME/CFS group (n=3)	**Control group (n=3)**	**ME/CFS group (n=3)**	**Control group (n=3)**
$V'O_{2\,max}$ (L/min)	1.34 ± 0.1	1.40 ± 0.3	1.27 ± 0.2	1.33 ± 0.2
$V'CO_{2\,max}$ (L/min)	1.34 ± 0.1	1.16 ± 0.2	1.26 ± 0.1	1.03 ± 0.0
HR (bpm)	139 ± 8.2	107 ± 7.8	135 ± 14	103 ± 3.2
RER ($V'CO_2/V'O_2$)	1.03 ± 0.1	0.86 ± 0.1	1.01 ± 0.1	0.79 ± 0.1
RPE (1-10)	6 ± 1.0	2 ± 1.0	5 ± 2.1	3 ± 1.5

Values are expressed as means ± standard deviation. VO_{2max}: maximal oxygen uptake; L/min: litres per minute; VCO_2max: maximal volume carbon dioxide expired; HR: Heart rate (beats per minute); RER: Respiratory exchange ratio; RPE: Rate of perceived exertion

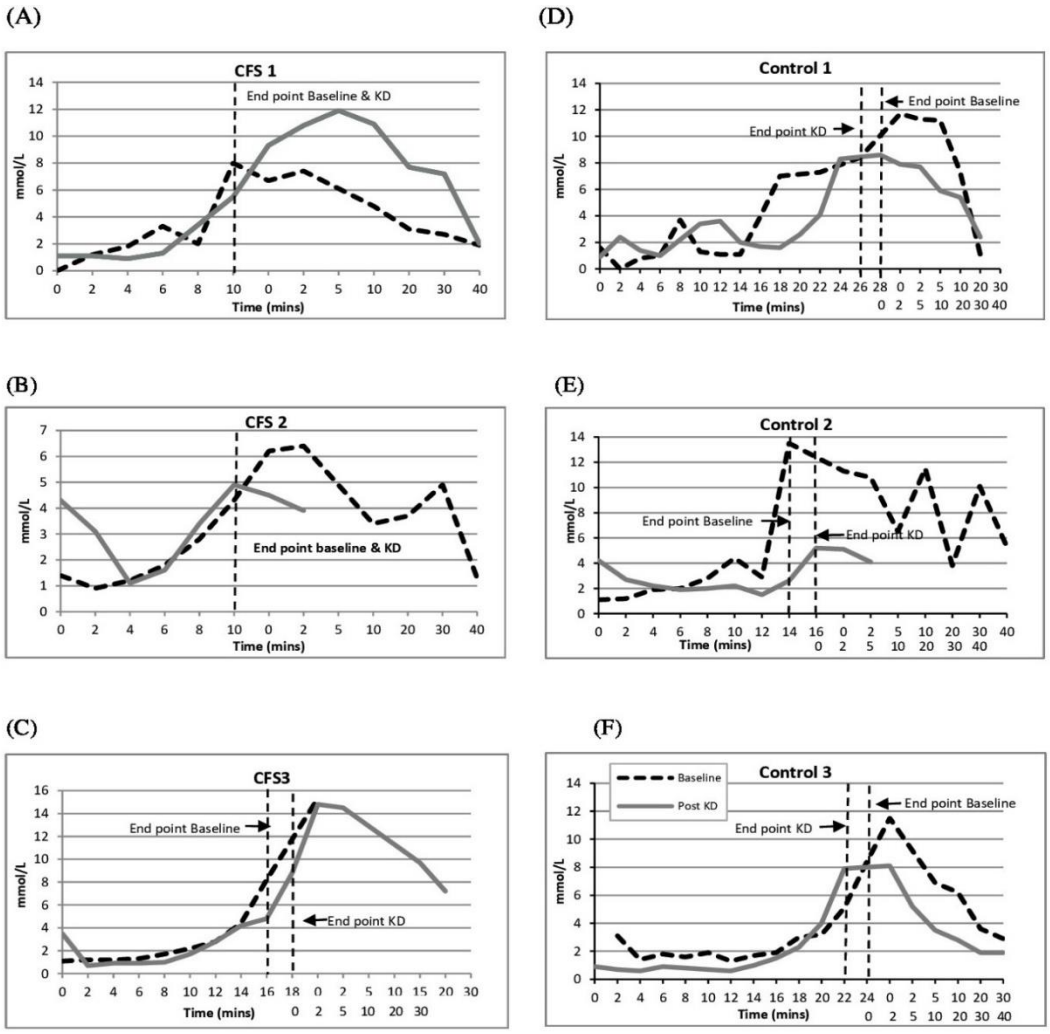

Figure 1: Individual lactate response during the physical activity test at baseline and post KD

DISCUSSION

Considering adherence to the diet in contrast to the controls, all three of the pwME/CFS followed the diet successfully, managing to limit their carbohydrate intake. From the process evaluation it showed the pwME/CFS accepted the diet more so than the controls and were all considering continuing the diet after completion of the study. There was a consensus that the diet had improved their symptoms, generally experiencing less feelings of fatigue, an improvement in energy levels and sustained cognitive ability. Importantly, we observed that the ketone diet normalised the high levels of glycolytic energy production during submaximal exercise activity in individuals with ME/CFS. Our findings suggest that ketone diet may enhance submaximal energy production during everyday activities and the impact of diet should be investigated on cognitive and physical functioning and levels of fatigue.

Feasibility and Adherence to the Ketogenic Diet

Figure 1 shows the macronutrient split of the individual dietary intake pre KD and on the KD, with missing data for Control 1. 80% (4 out of 5) of the participants successfully adhered to the KD, following the guidelines of <10% total energy intake and ≤50g carbohydrates per day with variation in each individual. However, only 3 out of 5 participants were in nutritional ketosis (≥0.5mmol/L) upon arrival on visit 2 (Table 3). The participant (Control 2) who did not successfully adapt their diet (39.2%/ 105g carbohydrate) had ketone levels of 0.5mmol/L, suggesting they were in nutritional ketosis. However, their calorie intake had reduced by 642kcal from baseline (1739kcal) to intervention (1097kcal) resulting in a reduction in energy intake compared to their estimated energy requirements (EER) of 2592kcal. Due to such a large energy deficit, the total energy and specifically the carbohydrates consumed were most likely utilised for energy production, after which point they may have entered a fasted state. In addition to the overnight fasting requirements this potentially induced increased the production of ketone bodies.

The two participants (CFS3 and Control 3) who had ketone levels <0.5mmol/L and were not considered to be in nutritional ketosis adhered well to the KD, successfully restricting carbohydrates to 5.5% and 7.2% of their total energy intake and were both within the <50g recommendation (Table 2) in accordance to the recommended guidelines shown in the participant information sheet. However, literature suggests that a well formulated KD not only consists of <50g of carbohydrates per day but also recommends a moderate protein intake of 1.5g/d per kilogram of body weight to successfully increase ketone levels [17, 18]. Suggestive that CFS3 and Control 3 exceeded guideline protein intake, which may have impacted on the production of ketone bodies. Furthermore, under carbohydrate restriction, the body metabolises protein producing glucose via gluconeogenesis [19]. Therefore, the excess protein intake may have been utilised as an energy substrate before lipid oxidation could take place due to the hierarchy of fuel selection under these conditions [20].

CPET (VO_{2max}) and Acute Physical Activity Response

As expected both pwME/CFS and the controls appeared to adapt to lipid metabolism measured by VO_2 and an increase in fat burning shown by lower CO_2 and lower RER at submax post KD (Table 3). If glycolytic metabolism is indeed impaired in pwME/CFS the KD may have potentially provided a metabolic shift in substrate utilisation that enabled an increase in physical activity capacity, enabling them to sustain the exercise stressor for a longer time period shown by an increase in performance time (Figure 1) and a decrease in RPE from baseline to post KD at submax (Table 3).

In this study, RER values produced by the controls suggest that they were utilising lipids at the 75W work rate in comparison to the pwME/CFS who were utilising carbohydrates at the same comparable work rate (Table 3). These results, alongside the reported hard rate of perceived effort, suggest the pwME/CFS were already working close to high levels of exertion at the 75W time point which agrees with findings by Snell *et al.* [21] who found pwME/CFS to have higher RER levels compared to healthy controls under similar conditions. In addition, Snell *et al.* [21] determined that the relationship between higher RER and higher RPE was therefore indeed a true reflection of effort and not just an unwillingness to continue to exercise, this indicates that the pwME/CFS were indeed closer to maximal exercise capacity before the controls. These findings correspond to the differences in performance time, with the controls collectively performing for longer compared to the pwME/CFS (Figure 1). According to Messonnier *et al.* [22] trained subjects have the capacity to oxidise lipids at a higher work rate than untrained subjects. With further studies showing those who are more physically active to have a lower RER in comparison to those who are more sedentary also at comparable workloads [23, 24]. Results from the IPAQ-SF obtained in this study placed the pwME/CFS in the moderate category for activity level, whereas the controls were in the high category indicating they were less sedentary. This suggests there may indeed be a relationship between RER and activity levels in these individuals.

Furthermore, when comparing heart rate (HR) in both pwME/CFS and the controls, the pwME/CFS had a higher HR, suggesting they were working to full capacity in both tests (Table 3). HR is generally related to cardiovascular fitness, exercise intensity and effort [25]. However, it is important to highlight pwME/CFS generally appear to have variability in HR even at rest compared to healthy controls [21]. Snell *et al.* [21] support the findings that RER is a better predictor of effort in pwME/CFS as it disregards any association to HR variability within this group, which can be further validated by Van Ness *et al.* [26] and Davenport *et al.* [27] who found pwME/CFS generally show a blunted HR response to exercise at high intensity.

When comparing the group acute physical activity responses from baseline to KD in this study (table 3) it showed both the pwME/CFS and the controls experienced a decrease in submaximal RER. Differences in the pwME/CFS were not as pronounced, but suggest that the KD could provide a metabolic shift in substrate utilisation. RER is an indirect measure of substrate utilisation relative to energy expenditure with values of ≥1.10 indicating that carbohydrates are being predominantly utilised, and lower values of <1.10 indicative of higher levels of fat oxidation. Furthermore, RER is also considered an objective measure of effort with peaks of >1.10 indicating higher exercise intensity, suggestive of time to fatigue and lower values of <1.10 indicating only submaximal effort [23, 24].

Figure 1 shows inter-individual variation of lactate output. Out of the pwME/CFS (Figure 1, A to C) one participant had an increase in lactate levels on the KD compared to baseline (A), one participant showed a decrease on the KD compared to baseline (B), whilst the third participant had a similar lactate response in both tests (C). Two of these participants (A and C) reached the same time point on both tests, suggesting that neither higher nor lower lactate levels impaired or enhanced exercise performance in these individuals with ME/CFS. The third participant with the similar lactate output (C) managed to exercise for an extra 2 minutes on the KD in comparison to baseline, again suggesting that lactate may have not been a limiting factor in exercise capability, however this individual produced ketone levels that were just under the threshold to be considered to be in nutritional ketosis (Table 2).

In the controls lactate levels decreased in all participants on the KD compared to baseline (Figure 1, D to F), with one participant experiencing much lower levels on the KD (E). However, there was a decrease in peak exercise performance time in all participants (D-F), each reaching exercise maximum 2 minutes earlier on the KD in comparison to baseline, correlating with an increase in RPE (Table 3).

This suggests that the KD impaired exercise performance in the controls with feelings of fatigue being experienced sooner, but indicates that lactate may have not been the limiting factor for this group. Ramos-Jimenez *et al.* [28] found lower lactate concentrations to be suggestive of higher rates of lipid oxidation due to the effects of physical activity increasing mitochondrial enzyme activity, driving fatty acid oxidation and relative to the reduction of RER. This could suggest that the KD may have effectively provided a metabolic shift in substrate utilisation in the control group, shown in this study by the decrease in RER from baseline to post KD intervention (Table 3). However, findings from Fleming *et al.* [29] demonstrated there to be a direct relationship between RPE and blood ketones following high fat diets which negatively impacted exercise capacity in non-trained individuals, supported by White *et al.* [30] who found blood ketone concentrations were directly related to feelings of fatigue.

The pwME/CFS produced lower VO_2 values (Table 3) at both baseline and post KD compared to the controls, indicating they had less aerobic capacity. Once maximal O_2 uptake is reached, anaerobic metabolism becomes the predominant metabolic pathway for energy production, resulting in the production of lactate and the onset of fatigue [20], this indeed corresponds with the results obtained in this study from the individuals, with the pwME/CFS reaching maximum capacity before the controls, with higher levels of lactate, RER and RPE. This has previously been demonstrated by Riley *et al.* [31] who found higher lactate concentrations, HR and RPE in pwME/CFS compared to controls at the same workloads. Importantly, if VO_2 is reached at much lower levels of O_2 consumption in pwME/CFS suggesting they are indeed more anaerobic, it could highlight a relationship between fatigue and symptom exacerbation and PEM experienced after only light exercise and/or activities of daily living if O_2 thresholds can be exceeded at such low levels [21].

Carbohydrate restriction is important to consider for all individuals performing exercise due to reduced tissues glycogen stores [32]. Following the KD intervention, the minimal carbohydrate intake may have impacted muscle glycogen stores with little or none available for energy. Once depleted, individuals would naturally find it difficult to sustain exercise, limiting physical performance and causing fatigue [33, 34]. However, it was predicted the ketones should have physiologically driven fat oxidation to provide energy, additionally further consequences of limited glucose availability involves a reduced capacity of the Krebs cycle for energy production relating to a limited availability of intermediates for fat oxidation [35].

Limitations

The ME/CFS sample used in the study cannot be considered representative of the population group as a whole, due to different levels of severity experienced in those with ME/CFS. Only individuals who were able to partake in the exercise test were included in the study, a difficulty experienced in previous research by Snell *et al.* [21]. This resulted in difficulty to recruit due to the nature of the exercise test possibly exacerbating symptoms and causing PEM in the pwME/CFS. However, the pwME/CFS that took part did not report any additional symptoms that were atypical of their condition following the exercise testing. The wash out period following the first test and commencement of the KD was used to ensure the participants had fully recovered and to differentiate between the possible adverse effects of the KD. This would be recommended for future work to ensure participant wellbeing and safety and to reduce the risk of participant drop out. Limited recruitment time resulted in low participation making it difficult to conclude at whether the KD had a significant effect on the population group nor is it representative to assume any benefits.

CONCLUSION

Data collected in this study enabled feasibility to be assessed specifically in relation to the testing methods used considering the possibility of limited exercise capacity in the ME/CFS group and further showed that compliance to the KD was obtainable to the majority of participants and in all participants with ME/CFS. Our findings suggest there may be potential changes in submaximal energy utilization, and further work to investigate these responses is now warranted to assess whether the use of ketones as an alternative energy substrate are beneficial in this condition, and to assess the potential of the KD in relation to symptom management.

Conflicts of interest: None

Authors' Contribution: JC, SC and HD were involved in the design and overall conduct of the protocol. JC, SC, YL and HD were responsible for the data collection. JC, SC and HD were responsible for the statistical/ data analysis and writing of the paper.

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