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Randomized Control Trials

Can a modified ketogenic diet be a nutritional strategy for patients with McArdle disease? Results from a randomized, single-blind, placebo-controlled, cross-over study

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SUMMARY

Background: McArdle disease is caused by myophosphorylase deficiency leading to blocked glycogenolysis in skeletal muscle. Consequently, individuals with McArdle disease have intolerance to physical activity, muscle fatigue, and pain. These symptoms vary according to the availability of alternative fuels for muscle contraction. In theory, a modified ketogenic diet (mKD) can provide alternative fuels in the form of ketone bodies and potentially boost fat oxidation.

Methods: This randomized, single-blind, placebo-controlled, cross-over study aimed to investigate if a mKD improves exercise capacity in individuals with McArdle disease. Participants were randomized to follow a mKD (75–80% fat, 15% protein, 5–10% carbohydrates) or placebo diet (PD) first for three weeks, followed by a wash-out period, and then the opposite diet. The primary outcome was change in heart rate during constant-load cycling. Secondary outcomes included change in plasma metabolites, perceived exertion, indirect calorimetry measures, maximal exercise capacity, and patient-reported outcomes.

Results: Fifteen out of 20 patients with genetically verified McArdle disease completed all study visits, and 14 were included in the data analyses. We found that the mKD induced a metabolic shift towards increased fat oxidation (~60% increase), and a 19-fold increase in plasma β-hydroxybutyrate ($p < 0.05$). The mKD did not improve heart rate responses during constant-load cycling but did improve patient-reported outcomes and maximal exercise capacity (~20% increase) compared to the PD.

Conclusion: The mKD did not alleviate all McArdle disease-related symptoms but did induce some positive changes. To date, no satisfactory treatment options exist other than exercise training. To that end, a mKD can be a possible nutritional strategy for some individuals with McArdle disease who are motivated to undertake a restrictive diet.

Clinical trial registration: clinical trials.gov: NCT04044508.

Abbreviations: AUC, area under the curve; KB, ketone body; mKD, modified ketogenic diet; LCKD, low-carbohydrate ketogenic diet; PD, placebo diet; PA, physical activity; FAO, whole-body fat oxidation; CHO, whole-body carbohydrate oxidation; AcAc, acetoacetate; β-HOB, β-hydroxybutyrate; VO_{2max}, maximal oxygen consumption; W_{max}, maximal workload.

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1. Introduction

McArdle disease (Glycogen storage disease type V) is an inborn disorder of glycogen metabolism in skeletal muscle. Individuals typically have a complete absence of the enzyme myophosphorylase responsible for muscle glycogen breakdown, manifesting in intolerance to physical activity (PA) and PA-induced muscle pain as the core symptoms, which often progress to muscle injury [1,2]. Muscle glycogen is the most important fuel for working muscle at high intensities and early stages of PA. Accordingly, PA tolerance varies as a function of the availability of alternative fuels. This is well illustrated by the "second wind" phenomenon in McArdle disease, which is characterized by the ability to increase work output after around 8 min of PA due to increased availability of free fatty acids (FFA) and hepatic-derived glucose [3,4].

There is no efficacious treatment for McArdle disease. Physical conditioning is beneficial and recommended [1,5]. Oral sucrose ingestion before exercise can alleviate muscle symptoms and blunt the second wind, but the effect is short-lived, unsuited for spontaneous PA, and, if used in excess, results in a too high caloric load and weight gain [6,7]. Fatty acid oxidation (FAO) is increased in individuals with McArdle disease compared to healthy controls, but an upper limit for maximal FAO occurs, preventing full compensation for the blocked glycogenolyses [4]. A low-carbohydrate ketogenic diet (LCKD) has attracted attention as a potential therapeutic option for individuals with McArdle disease. The scientific rationale for the LCKD in McArdle disease is to boost FAO and introduce ketone bodies (KBs) as an alternative fuel for contracting muscles [8–10]. The LCKDs contain low amounts of carbohydrates and high fat, ranging from the classical ketogenic diet with more than 90% fat to less stringent diets with less fat, e.g., the modified ketogenic diet (mKD) [11,12]. A LCKD simulates the physiological state of fasting, resulting in increased lipolysis, increased availability of FFA, and stimulation of ketogenesis (conversion of FFA to KBs (acetoacetate (AcAc) and β-hydroxybutyrate (β-HOB))) [13]. In extrahepatic tissues, β-HOB is converted to AcAc and then into two acetyl-CoA molecules that can enter the tricarboxylic acid cycle (TCA). Theoretically, a LCKD can provide an alternative fuel source available early during PA in persons with McArdle disease, which may offer protection from muscle injury during planned and spontaneous PA.

Despite the lack of evidence of the LCKD's potential in McArdle disease, many individuals with McArdle disease have already tried a LCKD. The patient organization "IamGSD" has implemented several initiatives to meet the patient demand [14,15], including starting a social media group, "ketosis in McArdle disease", with currently more than 1000 members. We have recently published a survey reporting that one-third of an international cohort of 183 individuals with McArdle disease had tried a LCKD, and 90% reported the diet to be beneficial [16]. The most reported improvements were on core symptoms of McArdle disease: PA-intolerance, PA-induced muscle pain, and fatigue. Weight loss was another positive effect. To date, two case stories have been published on the topic, both indicating effects with the LCKD [17,18]. Furthermore, we found in an open-label mKD pilot study [8], conducted as a forerunner for the present study, that the diet seemed to improve exercise capacity slightly and resulted in weight loss, and boosted FAO. However, controlled trials are needed to establish whether the effects are true or simply a placebo effect.

This randomized, single-blind, placebo-controlled trial aimed to investigate if a mKD, with a composition identified in our previous pilot study [8], can improve exercise capacity and induce a metabolic shift towards increased fat and KB metabolism in individuals with McArdle disease.

2. Methods

2.1. Ethical approval

The study was approved by the Ethics Committee of the Capital Region of Denmark (H-18013022) and listed on clinical trials.gov (NCT04044508) prior to inclusion.

2.2. Study design and randomization

We conducted a randomized, placebo-controlled, single-blind, cross-over study testing the potential effects of the mKD in individuals with McArdle disease. Participants completed two 3-week diet periods on a placebo diet (PD) and a modified ketogenic diet (mKD). Each diet period was initiated by 3–7 days of diet-escalation to minimize induction symptoms. The two diet periods were separated by a wash-out period of a minimum of 13 days (median: 22 days; IQR: 17.5–36 days). The diet sequence was randomized 1:1, by random draw, to start with either PD or mKD (Figs. 1 and 2). Participants were screened before randomization and assessed at test visits before and at the end of each diet period (Fig. 2).

2.3. Participants

The inclusion criteria were genetically verified McArdle disease and age between 18 and 80 years. Exclusion criteria were pregnancy, breastfeeding, and any prior or current medical conditions and or medication that, in the judgment of the investigator, would prevent the patient from safely participating (e.g., significant cardiac or pulmonary disease, porphyria or disorders of fat metabolism).

We recruited participants from the Copenhagen Neuromuscular Center (CNMC), Rigshospitalet, Denmark, and from the McArdle clinic at the National Hospital for Neurology and Neurosurgery, United Kingdom. Participants received oral and written information about the study, and all participants consented to participate in writing prior to inclusion. All trial tests in all participants were carried out at CNMC.

2.4. Intervention: placebo and modified ketogenic diets

Both interventional diets (PD and mKD) were isocaloric and tailored to provide a daily energy intake close to estimated energy requirements, calculated as described by Mifflin-St Jeor [19] multiplied with a basic activity factor [20] (Table 1). Participants were instructed to follow a meal plan (Supplements S1) that was identical for the two diets and included 3 meals and 1–2 snack(s). Each meal consisted of 1 protein, 2–4 carbohydrate, and 2–3 fat choices chosen from an ingredient list (Supplements S2). At every meal and snack, the participants had to consume a carefully measured amount of a blinded liquid-supplement, which accounted for approximately 67% of the daily caloric intake. The macronutrient distribution in the mKD was based on the findings in a previous pilot study [8]. The first included participants (phase 1) were assigned to the mKD#1 and a PD#1 containing: ~75%/15%/10% and ~45%/15%/40% fat/protein/carbohydrates, respectively. Preliminary analyses revealed that some of the participants' plasma KB-levels were in the lower end. Therefore, we decided to increase the fat content of the interventional mKD for the remaining participants (phase 2) to a macronutrient distribution to mKD #2: ~80%/15%/5% fat/protein/carbohydrates, and correspondingly the PD distribution changed to PD#2: 50%/15%/35% fat/protein/carbohydrates.

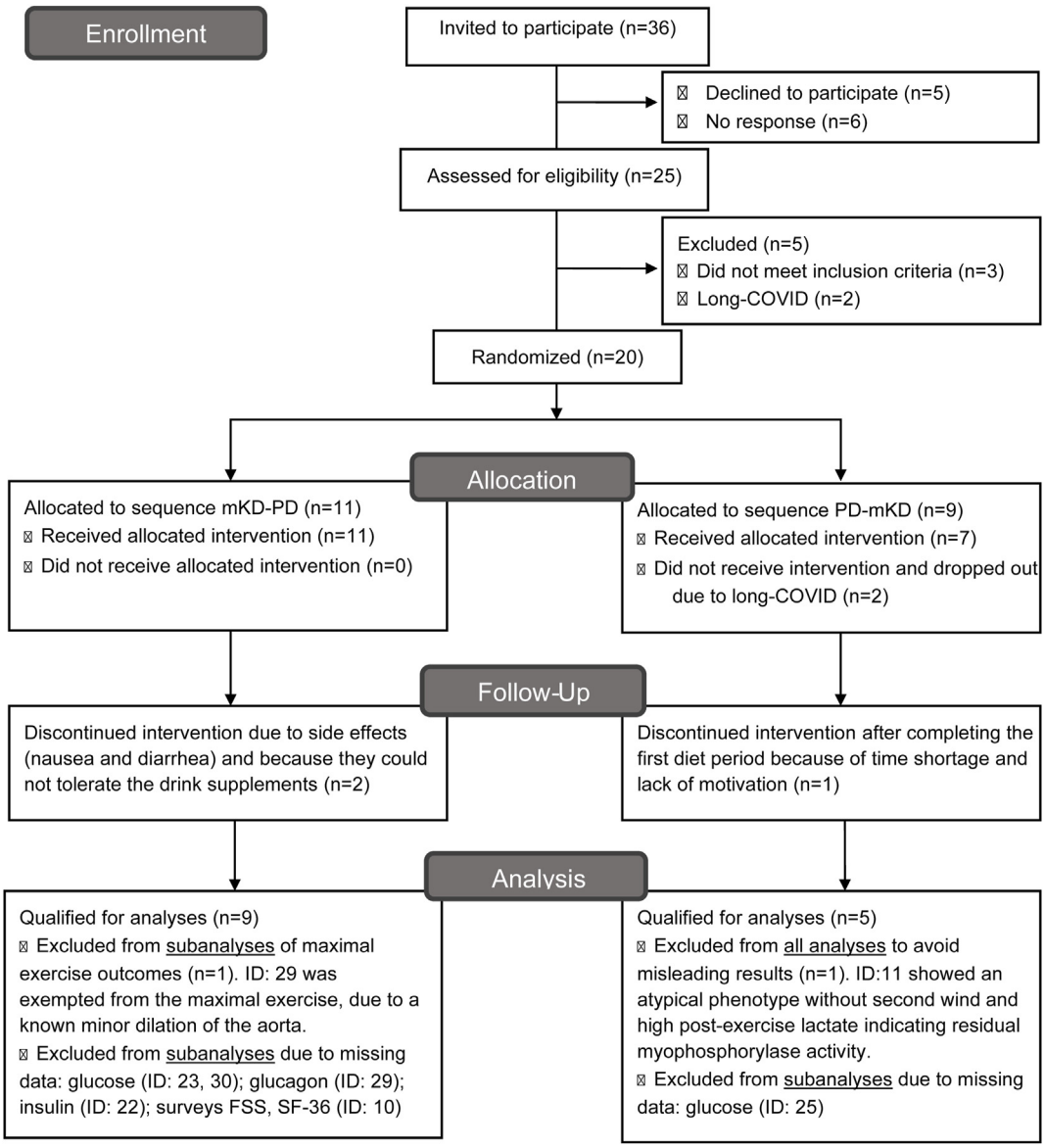

Fig. 1. Participant flow. n: number of participants; mKD: modified ketogenic diet; PD: placebo diet.

Compliance was assessed using a diet diary where all meals, adverse effects, and deviations were recorded. At the end of each diet period, the participant had to tick in the diary which diet they thought they had followed (mKD or PD). Ongoing dietary support was provided. At inclusion, the participants were encouraged to maintain the same activity level throughout the study.

2.5. Blinded supplement

Both liquid-supplements are nutritionally complete products containing oils, milk protein, supplemental amino acids, carbohydrates, vitamins, minerals, trace elements, and fibers. The mKD liquid-supplement: Ketocal 4:1 LQ (150 kcal/100 mL, 88.7%/8.2%/1.6%/1.5%, fat/protein/carbohydrates/dietary fibers) (Nutricia®). The PD liquid-supplement: Fortini (150 kcal/100 mL, 41%/9%/50%, fat/protein/carbohydrates) (Nutricia®) (see Nutricia's webpage for full ingredient lists).

Blinding process: Both supplements were over-labeled. The over-labeling was handled in part by the study group (NL, KLR) (phase 1) and in part by Nutricia (phase 2). The over-labeled products were labeled with liquid X or Y, respectively. Distribution into new identical containers would have been superior but impossible due to durability issues. The participants and the investigator responsible for coaching the patients during the exercise tests were blinded to the supplement. It was not possible to blind the rest of the study group.

2.6. Experimental protocol

The screening visit included an incremental cycle exercise test to exhaustion, as previously described [21]. If the participants had completed such a test less than 12 months before and had not changed habits, those test results were re-used.

At test visits, the participants arrived overnight-fasted and had an isocaloric breakfast, which at baseline visits consisted of: a bun, butter, cheese, jam, and apple, and at the end of each diet intervention was tailored to follow the prescribed diet. Next, a cubital venous catheter was inserted for blood sampling. Approximately

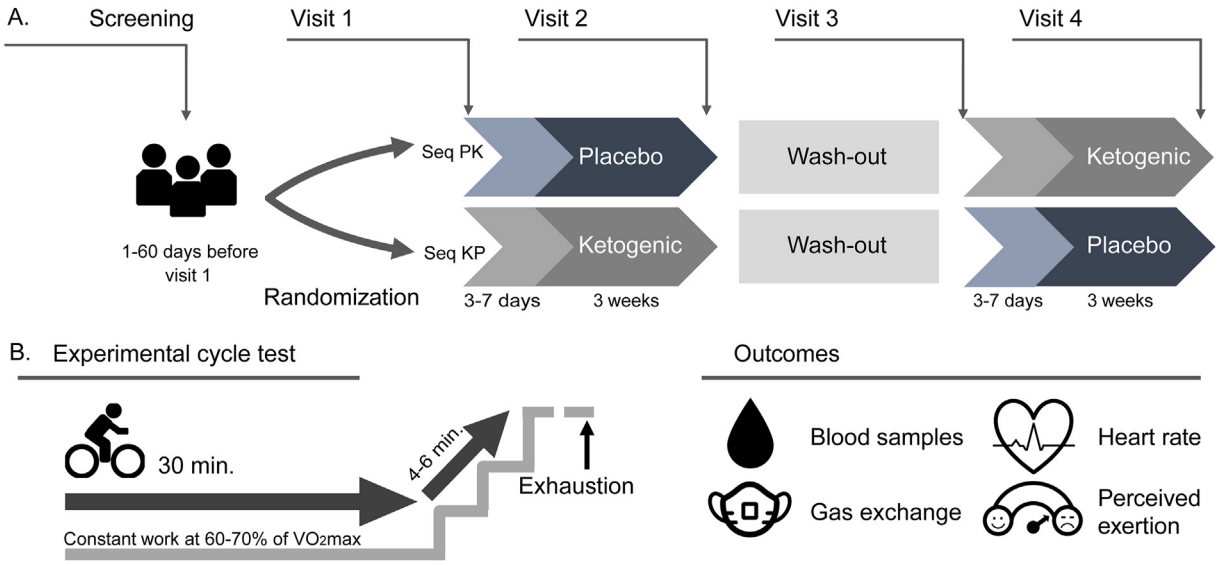

Fig. 2. Study design (A) and experimental cycle test protocol and exercise outcome measures (B). Seq. PK: sequence placebo then ketogenic diet; Seq. KP: sequence ketogenic then placebo diet; HR: heart rate; PE: perceived exertion; min: minutes; VO_{2max}: maximal oxidative capacity.

Table 1
Participant demographics.

ID	Country	Diet #	Calories mKD/PD	Sex (M/W)	Age (years)	PYGM variants	BMI	Compliance mKD/PD (%)
01	DK	1	2240/2220	M	43	c.482G>A (homo)	24.4	92.0/77.0
02	DK	1	2240/2220	M	27	c.148C>T, c.2262del	22.6	97.4/100
03	DK	1	2240/2220	M	65	c.148C>T, c.2262delA	24.0	98.8/95.5
04	FO	1	1910/1890	F	25	c.148C>T (homo)	26.2	100/100
06	*DK*	*1*	*1910/1890*	*F*	*51*	*c.148C>T, c.2392T>C*	*33.9*	*NA*
07	FO	1	2240/2220	M	54	c.148C>T (homo)	26.7	97.6/98.0
08	FO	1	1910/1890	F	42	c.148C>T (homo)	29.8	96.0/83.3
09	*DK*	*1*	*2240/2220*	*M*	*53*	*c.148C>T, c.2392T>C*	*35.3*	*NA*
10	DK	1	1910/1890	F	44	c.2262del, c.661-601G>A	28.8	96.4/97.6
11	***DK***	***1***	***2240/2220***	***F***	***41***	***c.148C>T, c.1094C>T***	***48.1***	***NA***
20	*UK*	2	*NA*	*M*	*32*	c.148C>T, *c.613G>A*	*29.6*	*NA*
21	*UK*	*2*	*NA*	*M*	*28*	c.148C>T, *c.613G>A*	*39.1*	*NA*
22	UK	2	2260/2210	M	57	c.148C>T (homo)	30.1	95.2/100
23	UK	2	2260/2210	M	60	c.148C>T, *c.613G>A*	32.0	95.8/96.4
24	*UK*	*2*	*NA*	*M*	*29*	*c.226delA (homo)*	*24.1*	*NA*
25	UK	2	2260/2210	M	58	c.148C>T, c.808C>T	26.4	100/100
26	IRL	2	2260/2210	M	42	c.148C>T, *c.613G>A*	29.0	98.2/92.6
28	UK	2	1780/1790	F	44	c.148C>T, c.1466C>G	21.8	95.6/95.8
29	IRL	2	2260/2210	M	59	c.148C>T (homo)	24.5	89.3/91.4
30	UK	2	2260/2210	M	60	c.148C>T (homo)	29.0	86.7/92.9
Mean ± SD[a]		7/7		M10:F4	48.6 ± 12		26.8 ± 3	96.6/96.9

Italic: highlights incompleters. Bold: highlights the excluded participant. mKD: modified ketogenic diet; PD: placebo diet; DK: Denmark; FO: Faroe Islands; UK: United Kingdom; IRL: Ireland; M: male; F: female; NA: not applicable.
[a] Mean of included participants.

two hours after breakfast, the participants exercised for 30 min on a cycle ergometer (Excalibur sport, Lode, Groningen, The Netherlands) at a constant workload corresponding to 60–70% of their maximal oxygen consumption (calculated from the maximal exercise test). After 30 min, we incrementally increased the workload every minute to exhaustion. Heart rate (HR) and perceived exertion (Borg scale) were noted every minute [22]. Blood samples were drawn at rest, 5, 10, 20, and after 29 min of exercise and at exhaustion. Gas-exchange rates were measured continuously by a breath-by-breath analyzer (Quark CPET, COSMED, Milan, Italy) to calculate the respiratory quotient (RQ) and fat (FAO) and carbohydrate oxidation rates (CHO) [23]. Maximal oxygen consumption (VO_{2max}) and maximal workload (W_{max}) were defined as the highest measured mean level over 30 consecutive seconds.

2.7. Outcome measures

The primary outcome measure was the between diet-difference in exercise tolerance judged by HR during submaximal cycle exercise. Other outcomes included the between diet-difference in perceived exertion, in indirect calorimetry measures (RQ, FAO, CHO), and in maximal exercise capacity (W_{max} and VO_{2max} presented as both the absolute values ($VO_{2max,abs}$: mL/min) and relative to bodyweight values ($VO_{2max,rel}$: mL/min/kg)). Other outcomes were the between diet-difference in plasma KBs (AcAc and β-HOB), plasma hormones (epinephrine, insulin, and glucagon), and plasma metabolites (ammonia, lactate, glucose, and FFA).

Patient-reported effects of the diet interventions compared to baseline were evaluated using a computed single-question "How

have your McArdle symptoms been this week?" with a 5-point response scale (1: much worse; 2: worse; 3: unchanged; 4: better; 5: much better). Other patient-reported outcomes included the between diet-difference in the validated questionnaires Fatigue Severity Scale (FSS) [24] and the modified Short-form Health Survey (SF-36) [25,26]. The FSS has nine statements relating to symptoms of fatigue, where higher scores point to higher fatigue levels. The SF-36 scores self-rated daily function divided into eight subdomains, where a score of zero is equivalent to maximum disability and a score of 100 to no disability [26].

2.8. Blood samples

We transferred blood to cooled EDTA (Ethylenediaminetetraacetic acid) containing tubes which were immediately spun at 1200*g* in a centrifuge at 4° Celsius for 10 min. Plasma was pipetted to cooled Eppendorf tubes and immediately frozen on dry ice, and stored at −80 °C until analysis. β-HOB, AcAc, lactate, FFA, and epinephrine were analyzed as previously described [8,10,21]. Ammonia and glucose were analyzed within 60 min from sampling (Cobas 8000, Roche Diagnostics, Mannheim, Germany, and ABL 90, Radiometer, Denmark, Copenhagen, respectively). When ammonia results failed, we reanalyzed ammonia from stored plasma [27]. Blood safety parameters were measured at all visits in the resting condition: low-, very-low- and high-density lipoprotein, triglycerides, total-cholesterol, creatine, glomerular filtration rate, potassium, sodium, creatine kinase, myoglobin, alanine transaminase, aspartate transaminase, urate, hemoglobin A1c, and amylase (Cobas 8000, Roche Diagnostics).

2.9. Sample size

We calculated that a sample size of 14 participants was required to detect a minimal relevant change in the primary outcome measure HR of ≥5 bpm and the secondary outcome measure VO_{2max} of ≥3 mL/kg/min. This would give 80% power and two-sided 95% confidence intervals around assumed mean values for each parameter. Based on previous studies in the same population, we assumed a standard deviation for HR of 5 bpm and 4 mL/kg/min for the VO_{2max} [5,6]. Because of the risk of dropouts with a diet intervention, we aimed to include 20 participants.

2.10. Statistical analyses

Values are presented as mean ± standard deviation (SD). To enable between-diet comparison, we calculated summary statistics. The physiological outcomes (HR and perceived exertion) were evaluated both pre-second wind (defined as the peak level pre-second wind) and post-second wind (defined as mean values during 10–20 min of submaximal exercise). The indirect calorimetry measures (FAO, RQ, and CHO) were evaluated both pre- (defined as mean values during 3–9 min of exercise) and post-second wind. For the blood samples, we calculated the area under the curve (AUC) to estimate the response for the whole exercise bout. Next, we subtracted the end-visits from the baseline-visits to calculate the delta-means (Δmean) and delta-AUCs (ΔAUC). Finally, we calculated the between-diet difference (Δmean_PD vs. Δmean_mKD or ΔAUC_PD vs. ΔAUC_mKD) with a paired T-test when data were normally distributed. The normality of the data was tested visually with quantile–quantile plots. Non-normal data were compared with the Wilcoxon Rank Sum test. A p-value ≤0.05 was considered significant.

We controlled for a sequence effect by comparing the mKD-PD and PD-mKD sequence groups with the Wilcoxon Rank Sum Test due to the small number of participants in the two groups. As we did not find a sequence effect for any of the outcomes tested (HR, perceived exertion, and $VO_{2max,rel}$) the data were pooled. We also compared the two subgroups: mKD#1 and mKD#2, with regards to the changes in the following outcomes: β-HOB, AcAc, HR, perceived exertion, $VO_{2max,abs}$, W_{max}, weight, FSS, and McArdle symptom-score, and we found, that the only outcome that differed was a higher AcAc with the mKD#2 ($p = 0.028$), why we decided to pool all the data in subsequent analyses.

Statistical analyses were conducted in R (R v.4.1.0, Foundation for Statistical Computing, Vienna, Austria) and SPSS (IBM SPSS Statistics, v. 25, N.Y., USA).

3. Results

3.1. Participants

Figure 1 shows the participant flow. Participants were invited in two phases due to COVID-related delay. Phase 1: July 2018–October 2020. Phase 2: September 2021–October 2022. We included 20 participants, of whom 15 completed all study visits, and 14 were included in the data analyses (Fig. 1). Participant 29 was exempted from the maximal exercise (Fig. 1). Table 1 shows the participant baseline demographics. The participants completed the tests as described in the protocol, except participant 01, who at the mKD baseline-visit stopped the cycle test prematurely after 16 min due to muscle pain and discomfort.

3.2. Diet compliance and adverse effects

The participants demonstrated good compliance with the prescribed diets based on their self-reporting in the diet diaries (Table 1). Ten out of the fifteen participants (completing both diet regimes) could tell what diet they were on. Both diets were overall well tolerated. With the mKD: fatigue, headache, nausea, and diarrhea/constipation were commonly reported as mild and transient. With the PD-regime: constipation and fatigue were commonly reported. One participant had a presumed episode of mild rhabdomyolysis after the PD-baseline exercise test, which did not require hospitalization, and with full recovery after two days. No serious adverse events were reported. Two participants received penicillin during the trial, and one got COVID, all deemed unrelated to the diet interventions.

3.3. Primary outcome – heart rate

We found the typical second wind response at all four visits (Fig. 3A). At peak pre-second wind, the mean HR dropped numerically by −6 and −4 bpm with the mKD and PD, respectively, compared to baseline visits (Fig. 3A–B and Table 2). These changes were insignificant ($p = 0.10$ and $p = 0.24$, respectively), and there was no between-diet difference ($p = 0.64$). Furthermore, there was no difference between baseline and end-visit in the post-second wind period and no between-diet difference ($p > 0.05$) (Fig. 3A and Table 1).

3.4. Secondary outcomes

3.4.1. Perceived exertion

We found significantly lower perceived exertion at peak in the pre-second wind period with the mKD compared to baseline ($p = 0.003$) (Fig. 3D, E and Table 2). The same trend was found for the PD ($p = 0.15$). There was no between-diet difference. In the post-second wind period, there was no change in perceived exertion with the diets compared to baseline visits, and we found no between-diet differences ($p > 0.1$) (Fig. 3D, F and Table 2).

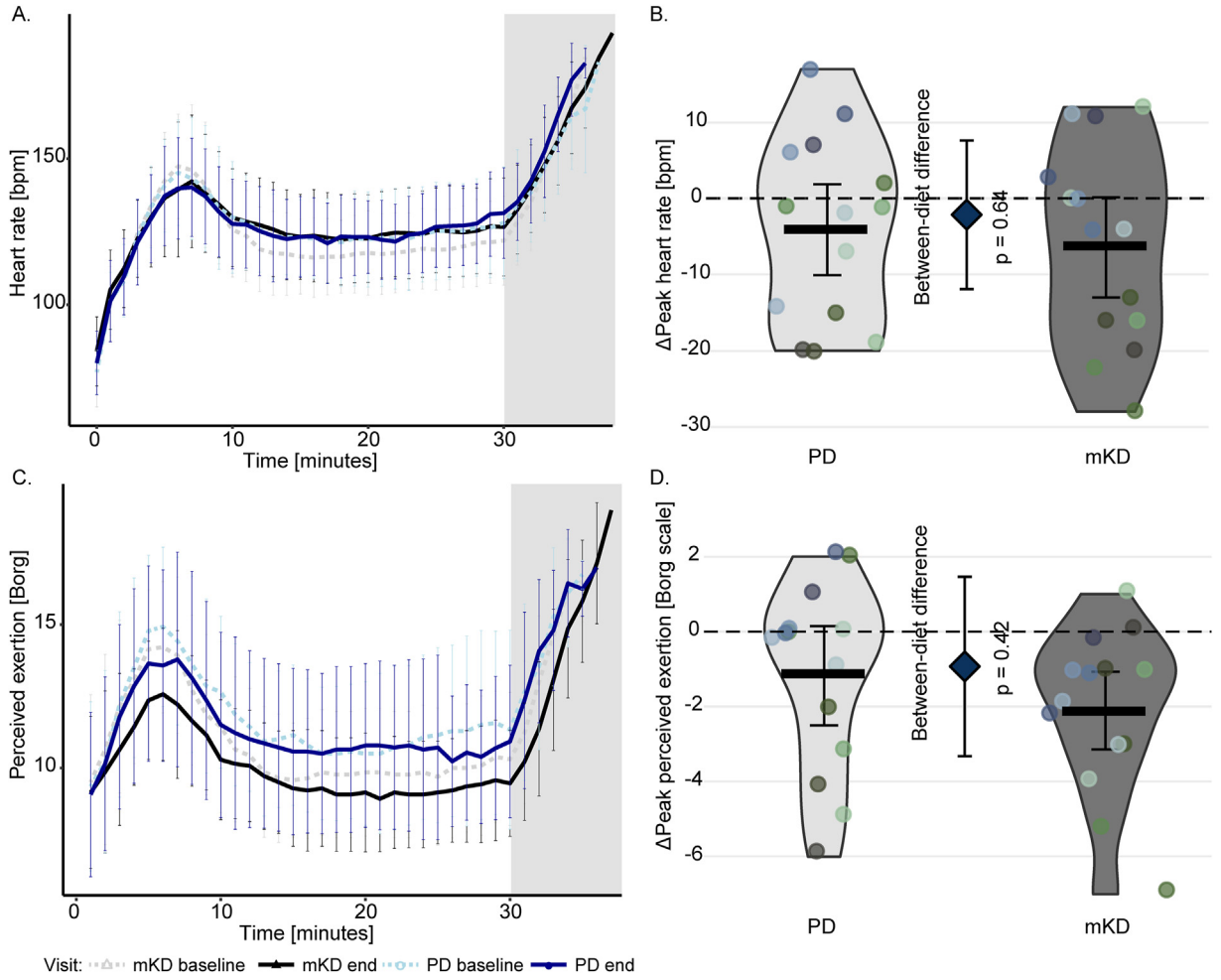

Fig. 3. Heart rate (A) and perceived exertion (C) during the exercise test at the four test visits. The gray shades illustrate the ramp to exhaustion. Values are mean ± SD. (B) and (D) are violin- and dotplots illustrating the delta (Δ: end-baseline) peak HR and perceived exertion values in the pre-second wind period for both diets. Points represent individual participant data, while the violin illustrates the diet-wise distribution of change. Horizontal bold lines indicate the mean change according to group, with the error bars indicating the 95% confidence interval. The mean between-diet difference with a 95% confidence interval is represented by the diamond shaped point and error bars located between the two violin shapes. PD: placebo diet; mKD: modified ketogenic diet; bpm: beats per minute.

3.4.2. Indirect calorimetry

The results from the indirect calorimetry measures are presented in Fig. 4 and Table 2. The FAO-rates were higher and the CHO-rates and the RQ lower on mKD compared to baseline and the PD in both the pre- and post-second wind period ($p < 0.00001$). There was no difference in indirect calorimetry measures on PD vs. baseline.

3.4.3. Maximal exercise capacity and body weight

We found that the mKD significantly increased the relative VO_{2max} by 11.6% compared to baseline and 20.1% compared to PD (Fig. 5A–B and Table 2), while VO_{2max} was unchanged on PD vs. baseline. The same significant improvements in W_{max} were found for mKD but not PD (Fig. 5C). The maximal HR did not significantly differ between mKD and baseline, and there was no between-diet difference ($p > 0.1$) (Table 2). The participants lost weight on both diets but significantly more on mKD vs. PD (Fig. 5D).

3.4.4. Plasma metabolites

The mean plasma concentrations of the metabolites during the exercise test are presented in Fig. 6. The mean β-HOB concentration increased 18.7-fold and AcAc increased 15.7-fold on mKD compared to the baseline visit (Fig. 6A–B). The between-diet differences (ΔAUC_{mKD} vs. ΔAUC_{PD}) confirmed a significant increase in the KBs on mKD compared to PD (β-HOB ($p = 0.002$) and AcAc ($p = 0.018$)). Post-hoc Pearson correlation analyses revealed no correlation between the β-HOB concentration reached on mKD and the change in peak HR ($\Delta Mean_{peakHR}$) ($p = 0.80$).

The FFA- and glucose concentrations also increased on mKD compared to PD, while plasma lactate was lower ($p \leq 0.05$) (all calculated as the difference in the ΔAUC_{mKD} vs ΔAUC_{PD}) (Fig. 6C–E). The ammonia concentrations tended to be lower on mKD compared to PD and baseline visits. However, the between-diet difference was not significant when looking at the whole exercise period ($\Delta AUC_{mKD,ammonia}$ vs. $\Delta AUC_{PD,ammonia}$) ($p = 0.36$) (Fig. 6D).

3.4.5. Hormones

We found lower insulin concentrations ($\Delta AUC_{insulin}$) ($p = 0.002$) on mKD compared to PD (Fig. 7A). On average, glucagon ($\Delta AUC_{glucagon}$) tended to be higher on mKD compared to PD ($p = 0.055$) (Fig. 7B). There was no between-diet difference in the epinephrine response ($AUC_{epinephrine}$) ($p = 0.24$) (Fig. 7C).

3.4.6. Safety parameters

The only significant change in the safety parameters with the diet interventions compared to baseline visits was a decrease in

Table 2
Results.

Exercise test	Modified ketogenic diet		Placebo diet	
	Baseline	End	Baseline	End
Peak HR_{2wind}	152 ± 18	146 ± 21	149 ± 18	145 ± 16
$HR_{post2wind}$ (beats/min)	119 ± 14	125 ± 15	124 ± 14	124 ± 14
Peak PE_{2wind}	15.1 ± 2.3	13.1 ± 2.4*	15.6 ± 2.7	14.5 ± 3.6
$PE_{post2wind}$ (Borg scale)	10.1 ± 2.1	9.5 ± 1.9	11.1 ± 2.2	10.8 ± 2.9
$FAO_{pre2wind}$ (μmol/kg/min)	**14.6 ± 4.0**	**22.2 ± 4.0***	**14.5 ± 4.2**	**13.8 ± 4.0**
$FAO_{post2wind}$ (μmol/kg/min)	**12.4 ± 3.2**	**19.8 ± 4.3***	**14.3 ± 4.8**	**13.0 ± 4.3**
$CHO_{pre2wind}$ (μmol/kg/min)	**46.5 ± 14.8**	**17.7 ± 11.1***	**48.5 ± 18.5**	**48.3 ± 16.2**
$CHO_{post2wind}$ (μmol/kg/min)	**60.5 ± 16.4**	**33.2 ± 12.9***	**58.0 ± 15.5**	**57.8 ± 10.0**
$RQ_{pre2wind}$	**0.83 ± 0.04**	**0.75 ± 0.03***	**0.83 ± 0.04**	**0.84 ± 0.04**
$RQ_{post2wind}$	**0.86 ± 0.03**	**0.79 ± 0.03***	**0.85 ± 0.04**	**0.86 ± 0.03**
$VO_{2max,abs}$ (mL/min)	**1803.9 ± 473.1**	**1933.5 ± 500.9***	**1707.9 ± 333.6**	**1615.7 ± 375.0**
$VO_{2max,rel}$ (mL/min/kg)	**21.6 ± 4.4**	**24.1 ± 5.1***	**21.0 ± 3.6**	**20.1 ± 4.2**
W_{max} (watts)	**97.3 ± 35.6**	**103.6 ± 35.4***	**88.0 ± 32.5**	**88.8 ± 32.2**
HR_{max}	172 ± 22	178 ± 17	169 ± 15	169 ± 19
Questionnaires	Baseline	End	Baseline	End
FSS	43.1 ± 12.4	36.5 ± 14.5*	39.5 ± 13.8	40.8 ± 14.5
SF-36 – Total	**65.7 ± 13.9**	**74.1 ± 16.1***	**72.3 ± 15.9**	**67.1 ± 18.6**
SF-36 – PF	**61.4 ± 9.9**	**71.2 ± 17.6***	**68.2 ± 19.7**	**67.1 ± 16.1**

Values are mean ± standard deviation (SD). *Illustrates significant difference between baseline and end-visits. Bold illustrates significant between-diet difference. HR: heart rate; PE: perceived exertion; 2wind: second wind; pre2wind: pre-second wind period (3–9 min); post2wind: post-second wind period (10–20 min); VO_{2max}: maximal oxidative capacity; abs: absolute; rel: relative; FAO: total whole-body fat oxidation rates; CHO: total whole-body carbohydrate oxidation rates; RQ: respiration quotient; FSS: Fatigue Severity Scale; SF-36: the modified Short-form Health Survey; PF: physical functioning.

total cholesterol and low-density lipoprotein on both mKD and PD. The creatine kinase (CK) levels varied a lot with no clear pattern regarding test visits (mean: 1878 U/L, range: 202–19.500 U/L).

3.4.7. Patient-reported outcomes

All the SF-36 domains tended to increase on mKD compared to PD. Significant changes were found for the domains: physical functioning ($p = 0.019$), role limitations due to emotional problems ($P = 0.009$), and emotional well-being ($p = 0.012$), as well as for the total score ($p = 0.008$) (Fig. 8C). The FSS-score decreased on mKD compared to baseline ($p = 0.013$), as opposed to no difference on PD compared to baseline ($p = 0.27$). Nevertheless, there was no statistical between-diet difference in the FSS-score changes (Fig. 8A). Figure 8B shows the results from the patient-reported effects on McArdle symptoms evaluated on the simple 5-point response scale. We found that their symptoms improved on the mKD vs. PD ($p = 0.031$).

4. Discussion

Individuals with McArdle disease report improvements in disease-related symptoms on different LCKDs. However, the effects have never been investigated in a controlled setup [8,16–18]. We conducted this randomized placebo-controlled trial as a direct consequence of the increasing patient-led demand to investigate if a mKD is a suitable nutritional strategy for individuals with McArdle disease.

The main findings of the present study are that three weeks on a mKD do improve patient-reported outcomes, with significantly more participants rating their McArdle disease-related symptoms as improved on the mKD vs. PD. This finding was corroborated by improvement of SF-36 subdomains and partly by the improved FSS scores, which improved on the mKD compared to baseline but did not differ between diets. Other main findings were that the mKD improved maximal exercise capacity and induced weight loss and a metabolic shift towards increased fat oxidation. However, the mKD did not improve submaximal exercise tolerance convincingly, as judged by the primary outcome HR.

The reasons for the patient-reported improved effects of mKD could be related to the metabolic shift towards fat (and ketone oxidation) in the participants compared to baseline and PD. We found lower RQ, increased whole-body FAO rates, and conversely lower CHO rates. These findings are further supported by lower lactate- and higher glucose levels indicative of lower muscle glycolysis. All these metabolic findings were also observed in our previous pilot study [8]. Furthermore, the mKD significantly elevated the plasma KBs (β-HOB and AcAc) compared to the PD. KBs are readily oxidized in muscle [10], and we have demonstrated that KB-oxidation can be increased in individuals with McArdle disease [28]. In the present study, we presume that KB-oxidation rates were increased. Proof of increased KB-oxidation requires stable-isotope technique, the gold standard for investigating oxidation rates [10,28]. The RQ for oxidation of AcAc is 1.00 and 0.89 for β-HOB [29], and the effect of KB-oxidation is, therefore, a rise in the RQ. Thus, the increase in FAO and decrease in CHO may even be underestimated in the present study, as we did not correct the conventional equations to calculate FAO and CHO for the contribution of KB-oxidation, which could have introduced a small but systematic error [29]. It is well documented that individuals with McArdle disease have an exaggerated mobilization and oxidation of fat during exercise, along with an exaggerated mobilization of hepatic glucose, driven by an increased sympathoadrenal response to exercise [4,30]. The increase in FAO has been shown to reach a plateau despite the increasing availability of FFA [4]. Previous attempts to boost FAO further with intralipid infusion or triheptanoin oil supplementation in McArdle disease have failed to improve exercise tolerance [21,31]. In the present study, we succeeded in elevating FAO beyond the previously reached levels, however, seemingly only to a new plateaued level. Nonetheless, strategies that promote the availability of FFA and FAO are advantageous, especially if it results in increased total whole-body oxidation.

Maximal exercise capacity improved on mKD compared to baseline (11.6% $VO_{2max,rel}$ increase) and the PD (20.1% increase). In comparison, previous aerobic exercise interventional studies in this cohort found that 14-weeks and 8-months of 4–5 exercise sessions a week increased relative VO_{2max} by 14% and 44%, respectively [5,32]. The improvement in the present study could be caused by

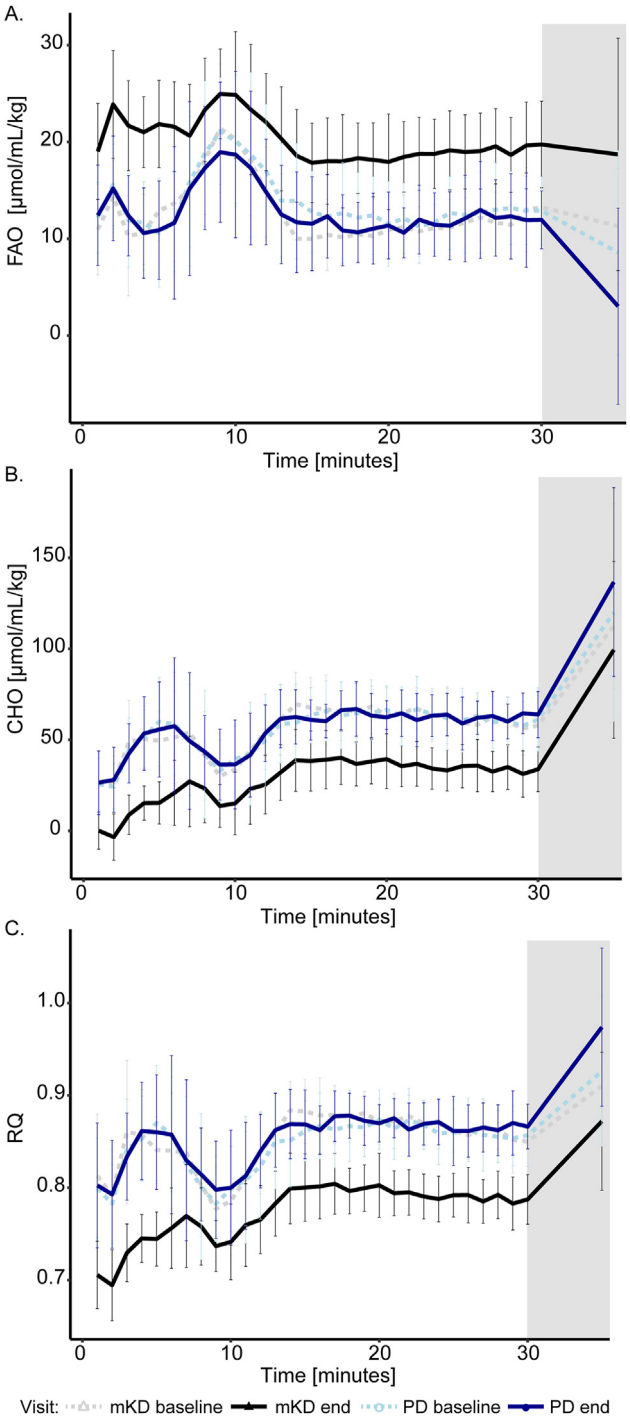

Fig. 4. Whole body fat- (A) and carbohydrate- (B) oxidation rates and respiratory quotient (C) during the exercise at the four visits. The gray shades illustrate the ramp to exhaustion. Lines are means and the error bars are one standard deviation. Full lines are end-visits, dotted lines are baseline-visits. FAO: fat-oxidation rates; CHO: carbohydrate oxidation rates; RQ: respiratory quotient; mKD: modified ketogenic diet; PD: placebo diet.

improved oxidative capacity due to increased availability of FFA and KBs and/or an improved ability to push oneself, which could have been induced by a central effect related to the enhanced ketone levels. As there was no difference in maximal HR, the results point towards an actual improvement of the oxidative capacity. This improvement was not driven by weight-loss alone either, as both the relative (per kg body weight) and absolute VO_{2max} increased. Improved maximal exercise capacity is an important functional finding in this cohort, as an increased VO_{2max} would increase function and raise the threshold for PA-induced muscle injury.

Submaximal exercise capacity was, however, not convincingly improved on the mKD compared to PD. We found numerically lower peak HR in the pre-second wind period on mKD compared to baseline visits, in line with the pilot study [8], but this was insignificant, and we found the same on the PD. Furthermore, the mKD did not abolish the second wind as seen using oral sucrose supplementation [6]. Perceived exertion is the subjective perception of exercise-induced exhaustion, which generally follows the HR response. In the present study, the perceived exertion was significantly lower at peak in the pre-second wind period on mKD compared to baseline, indicating that the participants found it easier to get through this challenging period. However, there was no between-diet difference in the perceived exertion response, why this effect remains dubious. Epinephrine- and ammonia tended to decrease on mKD, in line with the pilot study [8], which are directional changes suggesting improved exercise tolerance.

Although the elevated FAO rates, and assumed enhanced KB-oxidation, improved maximal exercise capacity, this was not enough to fully compensate for the blocked glycogenolyses during submaximal exercise and during the critical second wind. The reason for this could in part be because the KB-concentrations reached on mKD were in the lower end (mean 522, range: 103–1662 µmol/L), and only five participants exceeded the suggested lower limit indicative of ketosis (500 µmol/L) [13]. We can only speculate if higher levels of ketosis would have improved submaximal exercise capacity further in the participants. Interestingly, in the present study and in the pilot study [8], we did not find any correlation between KB-levels and the HR response. Another explanation for the insufficient improvement in submaximal exercise capacity could be the biochemical adage that fat, and likely also ketones, “burn in the flame of carbohydrates”, which refers to the anaplerotic intermediates from glycolysis needed to spark the TCA-cycle [4,28,33]. The blocked glycogenolysis will inevitably result in low TCA-cycle intermediates, which a LCKD will further reinforce [34]. Nonetheless, we did manage to increase maximal exercise capacity and FAO, so the lack of TCA-cycle intermediates can only be part of the explanation. Replenishing TCA-cycle intermediates, e.g., with anaplerotic triheptanoin supplementation while on a LCKD, is an interesting perspective. This is not well-investigated in humans. In a mouse model of familial Alzheimer's disease, triheptanoin supplementation to a LCKD effectively improved mitochondrial status [35]. However, triheptanoin supplementation has shown to be inefficient alone in individuals with McArdle disease [21].

LCKD regimes are popular and effective weight loss diets in the general population [13]. We found in a survey exploring the

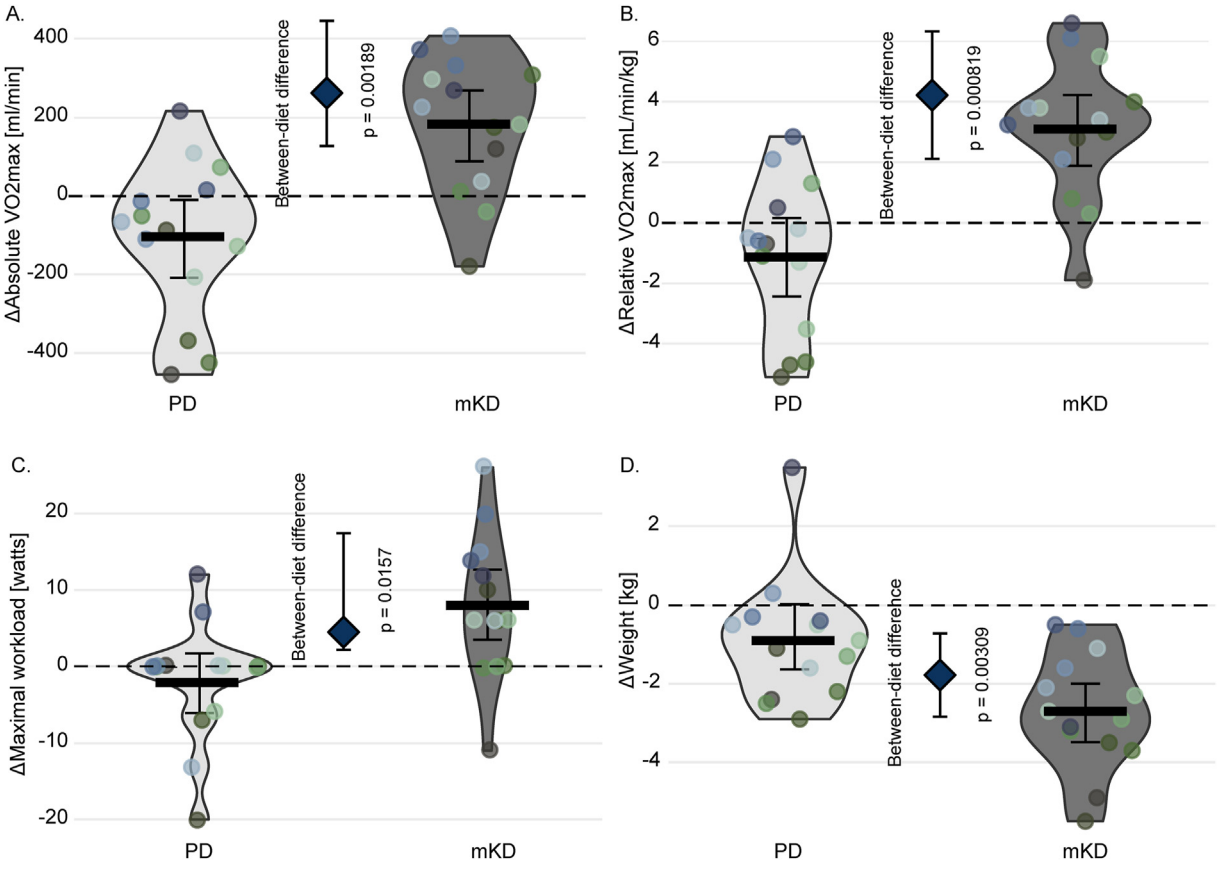

Fig. 5. Maximal exercise capacity and body weight. Violin- and dotplots illustrating the changes (end-baseline) in relative VO_{2max} (A), absolute VO_{2max} (B), maximal watts (C) and body weight (D) for the two diets. Points represent individual participants, while the violin illustrates the diet-wise distribution of change. Horizontal bold lines indicate the mean change according to group, with the error bars indicating the 95% confidence interval. The mean between-group difference with a 95% confidence interval is represented by the diamond shaped point and error bars located between the two violin shapes. VO_{2max}: maximal oxygen consumption.

patient-reported effects of a LCKD that 80% reported weight loss on the diet [16], supporting the finding of weight loss in the present study and the pilot study [8]. All pointing towards LCKDs are effective weight loss diets in this cohort, at least short term. Being overweight is a well-known issue in individuals with McArdle disease, which may be associated with less active lifestyles due to the physical activity intolerance and activity-induced muscle pain [2,16]. All these factors intertwine with one another, leading to a vicious cycle, and to that end alone, the LCKD could have its place.

4.1. Strengths and limitations

The primary strength of the present study is the randomized, placebo-controlled, single-blind design, which is challenging to design and conduct in a diet-interventional study. The PD was designed to resemble a standard diet as much as possible. However, it was impossible to reach the macronutrient composition of a standardized American diet. Furthermore, sticking to a strict diet is an intervention in itself. The PD could, therefore, potentially have caused metabolic changes that could mask the mKD effects. Another limitation is that we cannot guarantee that both drink supplements tasted identical – despite both having a 'neutral' taste. Since five of fifteen participants could not tell which diet they were on, we think that unblinding by taste was not an issue.

Compliance is a well-known issue with diet-interventions, and it is challenging to control for compliance in a blinded setup. Judged by the self-reports in the diet diaries, compliance in the present study was good. However, the relatively low KB-levels reached might be due to compliance issues. Another reason could be that the mKDs chosen were not strict enough. For that reason, we increased the fat-content of the mKD in phase 2, which we acknowledge as a study limitation. However, this change did not lead to significantly increased KB-levels or to other found 'diet-effects'. We chose to investigate mKD regimes in the present study as these diets better reflect what individuals with McArdle disease commonly report they have tried [16]. Stricter LCKD regimes, e.g., the classical KD, would ensure higher KB-levels, and would be theoretically interesting to test. However, it would probably not be

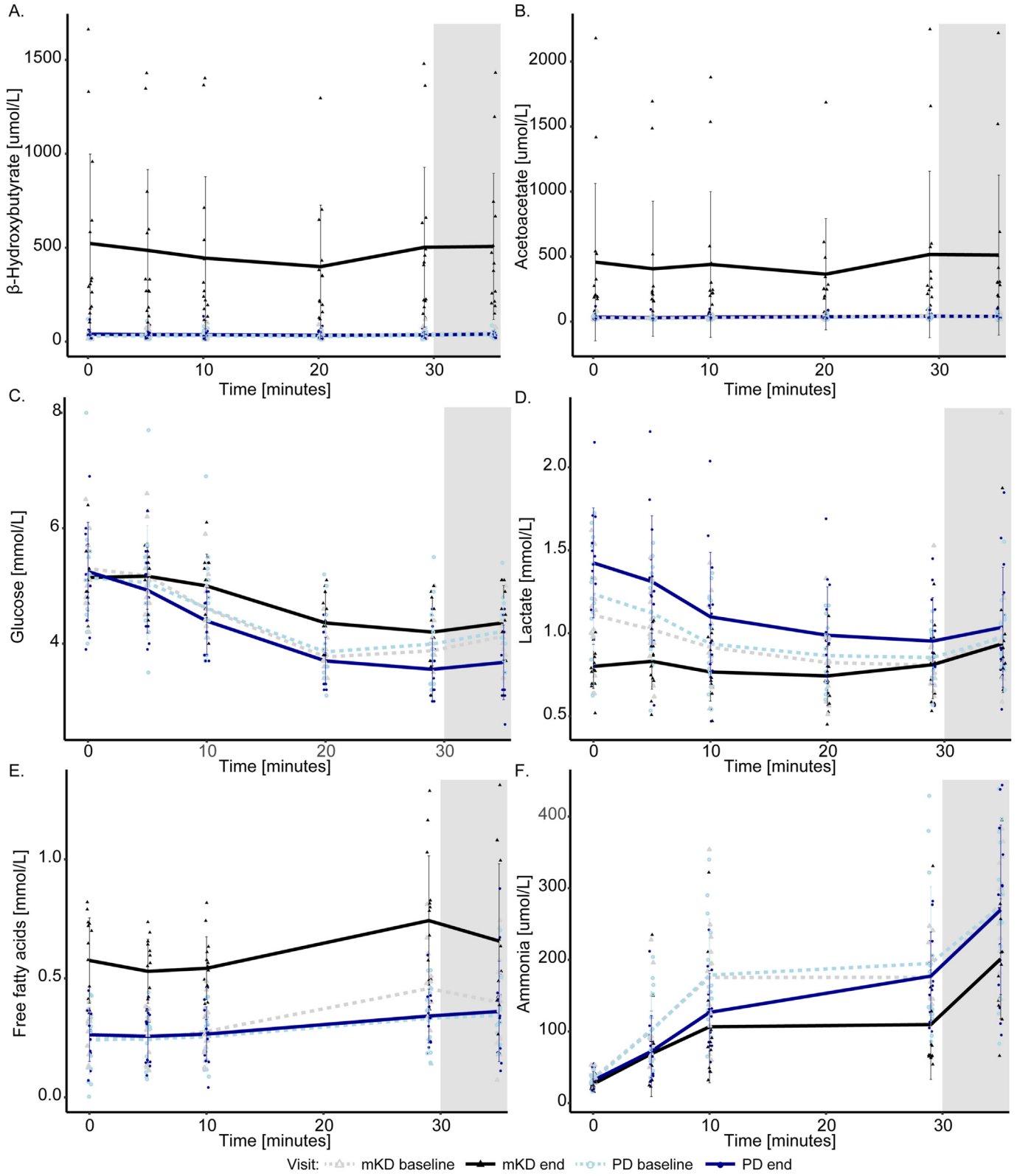

Fig. 6. Changes in the plasma metabolites β-hydroxybutyrate (A), acetoacetate (B), glucose (C), lactate (D), free fatty acids (E), and ammonia (F) during the cycle exercise test at the four test visits. The gray shades illustrate the ramp to exhaustion. Points represent individual participant data. The lines indicate the mean values, and the error bars are one standard deviation. mKD: modified ketogenic diet; PD: placebo diet.

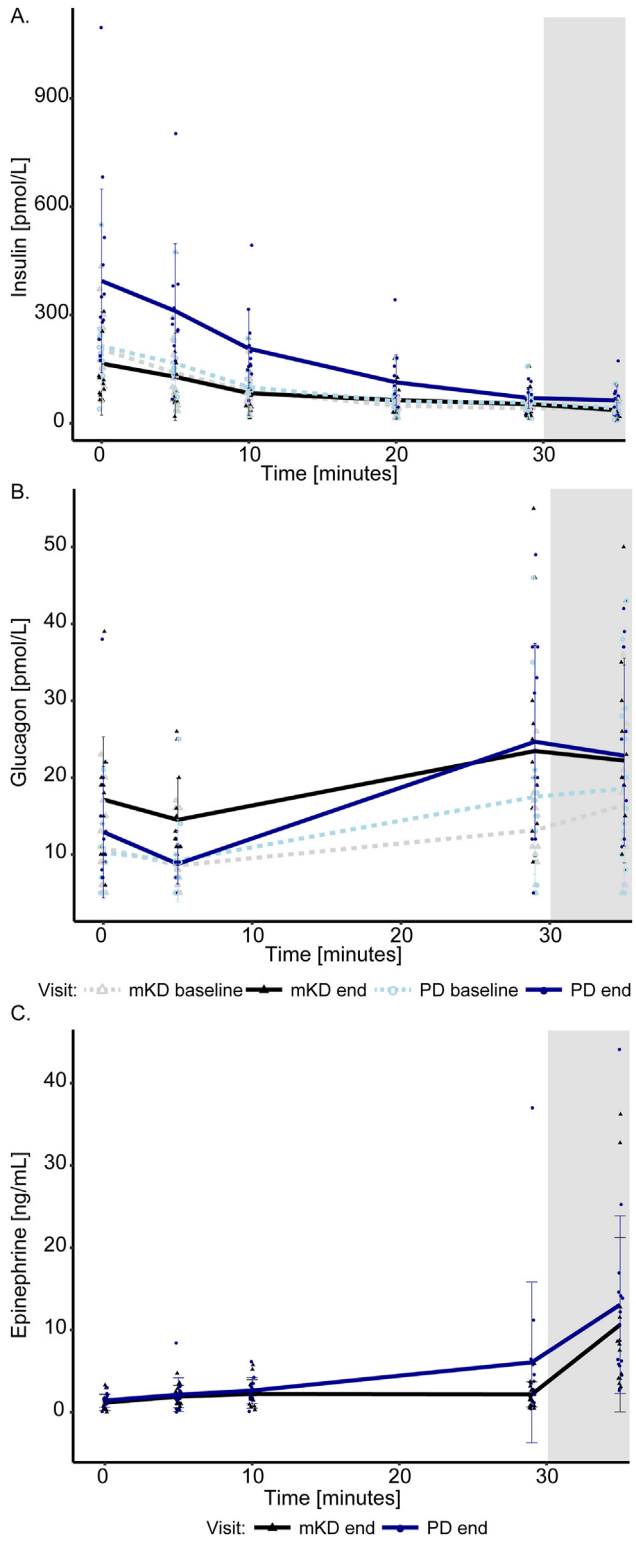

Fig. 7. Changes in the hormones insulin (A), glucagon (B) and epinephrine (C) during the cycle exercise test at the four test visits. The gray shades illustrate the ramp to exhaustion. Points represent individual patient data. The lines indicate the mean values and the error bars are one standard deviation. mKD: modified ketogenic diet, PD: placebo diet.

feasible for most, as it is extremely tough to follow. Another interesting topic is whether three weeks on a mKD, as applied in this study, is enough to ensure optimal keto-adaption. Keto-adaption is not a well-explored field, and the time for perfect keto-adaption is unknown. Phinney et al. first coined the term keto-adaptation, they showed exercise performance decreased after one week on a LCKD but drastically increased after six weeks compared to baseline, thus concluding that a LCKD requires an adaption of more than one week but possibly up to six weeks [36]. We induced a metabolic shift after only two weeks on a mKD in the pilot study [8] – indicating that three weeks should be enough to ensure some degree of keto-adaption. Future long-term studies are, however, still warranted to explore the dynamics of long-term keto-adaption in individuals with McArdle disease.

A limitation is the relatively small cohort completing the present study (n = 14), although power calculations were satisfied (primary outcome HR (n = 8) and secondary outcome VO_{2max} (n = 14)). Recruitment is challenging, when working with rare diseases, and in the present study we included all eligible patients in Denmark. The risk of selection bias can, therefore, not be excluded.

4.2. Recommendations based on the present study

The mKD applied in the present study improved patient-reported outcomes, maximal exercise capacity and induced weight loss and a metabolic shift with increased FAO-rates in participants with McArdle disease. Moreover, the mKD was only associated with a few mild adverse effects (primarily transient gastrointestinal complaints). The mKD failed to improve submaximal exercise tolerance – including the critical pre-second wind period. On that basis, the mKDs tested are not a sufficient treatment option for individuals with McArdle disease, and we encourage further research into potential other treatments for this disease. However, no other satisfactory treatment options exist to date, and to that end, the mKD can be a possible nutritional strategy for some individuals with McArdle disease.

It takes considerable effort to follow a LCKD [37]. The diet can be time-consuming and invasive for social life – especially in a family setting. Indeed we found in a survey that 21% found the diet effects and efforts balanced, 30% that the efforts exceeded the effects, and 43% found that the effects exceeded the efforts [16]. This highlights that a LCKD is not for all but worthwhile in almost half of this McArdle disease cohort, and therefore we argue that the diet is worthwhile considering in willing and motivated patients. Specialist dietetic guidance and support can possibly increase satisfaction with the dietary therapy and improve compliance [38]. Long-term use of LCKD regimes are not well described in the adult population, but LCKDs are mainly reported to be safe with mild adverse effects (mainly gastrointestinal complaints) [37]. Elevated cholesterols is another common side-effect, but may be modifiable with dietary adjustments [37,39]. The present study supports that three weeks on a healthy well-formulated mKD can even cause low-density lipoprotein reduction. Other rarer adverse effects are renal stones and gout. Future studies on long-term safety of LCKDs are warranted.

To ensure an optimal and healthy LCKD composition, compliance, and tolerability, we recommend that individuals with McArdle disease are referred to specialized units with physicians and dieticians with knowledge of this rare disease and LCKDs. We

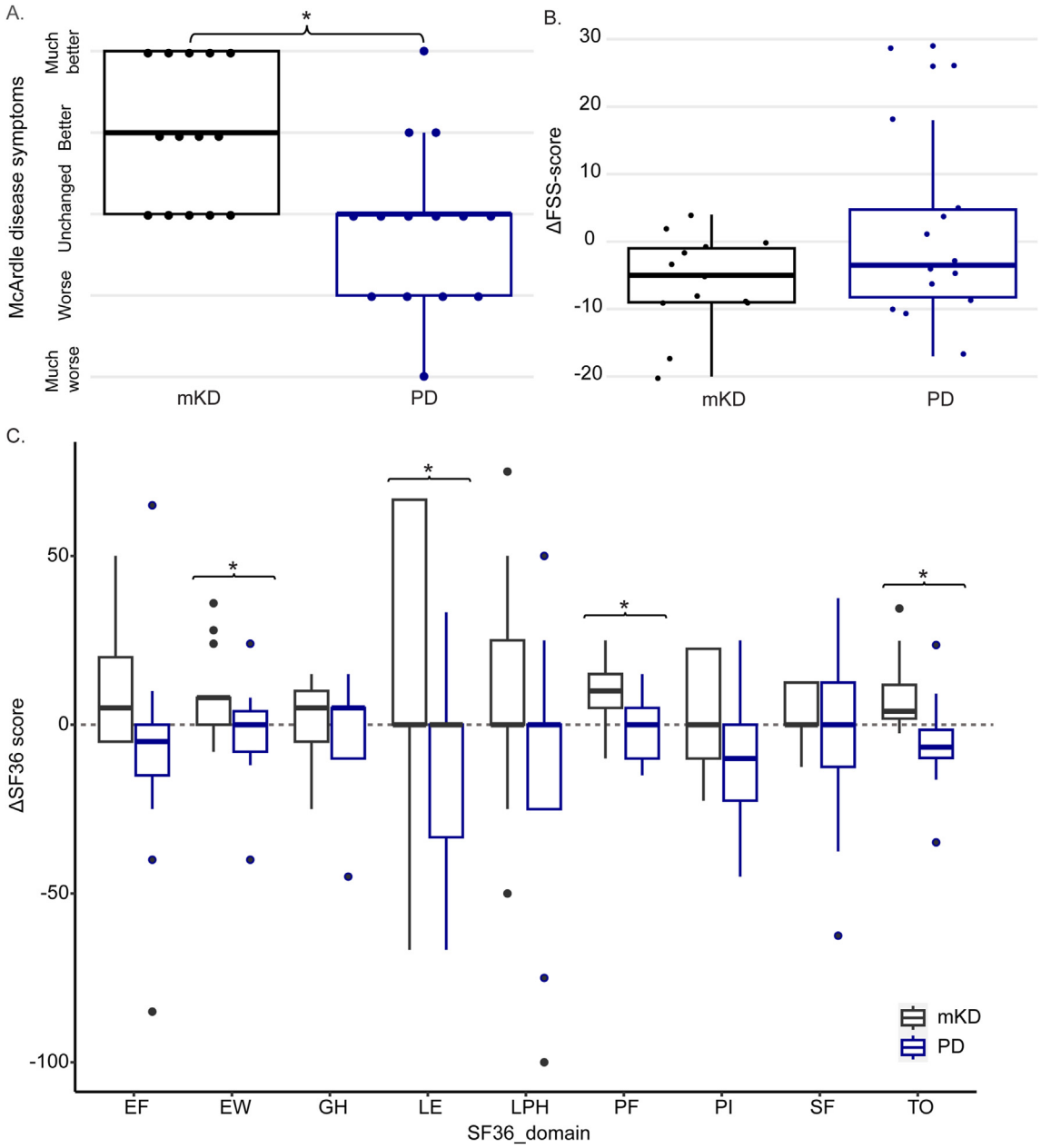

Fig. 8. Patient-reported outcomes. (A) shows boxplots of the change in symptoms with the two diets evaluated on a simple 5-point response scale ranging from much worse - too much better. (B) and (C) are boxplots illustrating the changes (Δ: end-baseline) for the FSS (B) and SF-36 (C) surveys for both diets. The asterisk indicates statistical significance ($p \leq 0.05$). FSS. Fatigue severity scale; SF-36: the modified Short-form Health Survey; mKD: modified ketogenic diet; PD: placebo diet; EF: energy/fatigue; EW: emotional well-being; GH: general health; LE: role limitations due to emotional problems; LPH: role limitations due to physical health; PF: physical functioning; PI: pain; SF: social functioning; TO: total score.

recommend a patient-tailored LCKD, which can be adjusted to reach the highest level of tolerability and compliance and be adjusted according to food preferences. The LCKDs are typically rich in animal-based nutrients, but animal welfare and climate impact should not be a barrier to starting a LCKD, as vegetarian and even vegan LCKD plans are possible to design. LCKDs can be very costly but should not be disregarded based on expenses, as proper dietetic counseling can help substitute costly food items with similar nutrition qualities to reduce costs [40,41].We recommend routine monitorization of potential long-term side effects and labs (including lipid profile). Lastly, we encourage future studies to explore the long-term use of a LCKD in McArdle disease.

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Data availability statement

Most data supporting this study are presented in this manuscript. Due to ethical concerns and GDPR regulations, supporting

data cannot be made openly available, but can be shared under some conditions upon request.

CRediT authorship contribution statement

Conceptualization: NL, CE, RQ, JV.
Funding acquisition/resources: NL, CE, RQ, JV.
Investigation: NL, MRN, MGS, CE, MM, KLR, AS, BK, GHB, FKE, GVH.
Analyses/visualization: NL, MRN, AS.
Writing original draft: NL.
Critical review/editing: All authors.
Supervision: RQ, JV.

Conflicts of interest

N.L. has received speaker honorarium from Nutricia, she reports no other conflicts of interest. The remaining authors report none.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.09.006.

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