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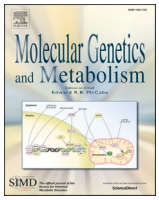

Research Paper

Ketogenic diet in adult patients with mitochondrial myopathy

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ABSTRACT

Background: This study aimed to explore the feasibility, safety and efficacy of a Modified Atkins Diet (MAD) in patients with mitochondrial myopathy (MM).
Methods: Patients with genetically proven mitochondrial disorder and exercise intolerance or muscle weakness followed a twelve week MAD. Feasibility was measured by diet duration and ketone levels. Safety was assessed by monitoring adverse events (AE). Efficacy was assessed by a maximal incremental test and a muscle performance test.
Results: Eight out of twenty patients completed the twelve week intervention. Reasons to discontinue were the occurrence of AE: rhabdomyolysis ($n = 3$), vomiting ($n = 1$), fatigue ($n = 6$), constipation (n = 1), in combination with a lack of improvement and adherence difficulties. On an individual level, various positive effects were reported including improvements in VO_{2peak} ($n = 6$), anaerobic threshold ($n = 9$), muscle fatigue resistance ($n = 5$), muscle strength ($n = 7$), fatigue ($n = 6$), glucose tolerance ($n = 7$), migraine ($n = 3$), sleep ($n = 3$), and gastrointestinal complaints ($n = 2$). Lipid profile improved and thirteen patients lost weight. All patients with mitochondrial DNA (mtDNA) deletions, experienced muscle related AE. The five patients with the m.3243A>G mutation achieved the longest diet duration.
Discussion/conclusion: MAD feasibility, safety and efficacy is variable in MD patients. MAD appears to be unsuitable for MD patients with mtDNA deletions. All patients should be monitored closely for adverse events when initiating the diet. Further research should focus on predictive factors to consider the diet, effectiveness of less stringent carbohydrate restricted diets.

1. Introduction

Mitochondrial diseases (MD) are a group of genetic disorders that are characterized by dysfunctional mitochondria. As a result, multiple organ systems are affected, with a pronounced impact on highly energy demanding tissues, such as brain, heart and skeletal muscle tissue [1,2]. MD exhibit significant phenotypic heterogeneity, wherein symptoms related to muscle function are categorized as mitochondrial myopathy (MM). In the absence of curative treatment, management is focused on symptom relief [3].

High fat, low carbohydrate ketogenic diets (KD) cause a shift in metabolism towards ketone body production in the liver. The Modified Atkins Diet (MAD) is a milder form of KD in which only carbohydrates are restricted (10–20 g/day) but not fat and protein, MAD is the most preferred form of KD for the adult population [4,5]. The ketone bodies are being converted into acetyl co-enzyme A, which can enter the Krebs cycle to be oxidized as a source of energy. The classical indication of treatment with KD is refractory epilepsy [6,7]. In addition,

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administration of a KD in a MD mice model induced mitochondrial biogenesis and slowed disease progression [8].

Research on the effects of KD in patients with MD is scarce [9]. In patients with mtDNA deletion(s) related myopathy, five patients had to stop KD within one week because of rhabdomyolysis [10]. However, rhabdomyolysis was not reported in a recent semi-randomized trial, evaluating efficacy and safety of KD for children with genetically proven MD [11].

A recent systematic review assessed the safety and efficacy of KD in genetically proven MD [12]. KD has led to improvement in seizure control in 7/8 MD patients with epilepsy and 3/10 patients reported improved muscle symptoms. In 4/20 cases, KD reversed the clinical phenotype (e.g. cardiomyopathy, movement disorder). However, adverse events (AE's) occurred in 13/20 individuals, including gastrointestinal discomfort, weight loss, nausea, headache, fatigue, rhabdomyolysis and dyslipidemia [12]. The authors concluded that no general recommendations on safety and efficacy of KD for MD could be made due to data scarcity and that prospective studies are necessary.

In this study, we aim to explore the feasibility, safety, and efficacy of a twelve week MAD intervention in a diverse group of adult patients with genetically proven MM.

2. Materials and methods

2.1. Study design

In this single center, single armed dietary intervention study, a twelve week MAD period was compared with a preceding two week period of regular diet. Adult patients (≥18 years) with genetically proven MD of the Radboudumc Nijmegen (the Nether lands) were invited to participate in this study. Measurements were performed during three study visits at the Radboudumc and at home at predetermined points in time (Fig. 1).

Inclusion criteria were presence of MM defined as exercise intolerance or muscle weakness Both are tested in the NMDAS. Mild exercise intolerance (NMDAS; section I question 9) is defined as symptomatic when inclining stairs. Mild myopathy (NMDAS; section II question 5) as minimal reduction in hip flexion and/or shoulder abduction only (eg Medical Research Council (MRC) 4+/5).

Exclusion criteria were serum creatine kinase (CK) levels above 1000 μ/l, a Body Mass Index (BMI) <20 kg/m^2, heart failure/pacemaker implementation, estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 (using the Modification of Diet in Renal Disease (MDRD)), (familial) hypercholesterolemia, antidiabetic medication, and inability to conduct maximal incremental cycle testing.

The study was approved by the Medical Ethical Committee Oost Nederland (2020 6614) and registered at the Dutch National Trial Register (NL74312.091.20).

2.2. Measurements

2.2.1. Complaints diary

Patients scored their adverse events in a complaints diary throughout the study. They had to report the occurrence, frequency and severity of complaints on a Numerical Rating Scale (NRS) from one to ten ([13], and they were asked to report any changes in medication use related to reported complaints.

2.2.2. Three day food records

Three day food records were used to check for diet adherence at five moments during the study period (Fig. 1). In the food records, all food and beverages consumed over two week days and one weekend day were listed. Intake was systematically calculated by Evry software® (Evry, Alphen aan den Rijn, the Netherlands) to determine energy (kcal), carbohydrates (g), protein (g) fat (g), fibre (g) and water (ml) intake.

2.2.3. Accelerometry

The Activ8® activity tracker (Activ8, Valkenswaard, the Netherlands) was used to determine Physical Activity Level (PAL) by measuring the average Metabolic Equivalents of tasks (METs) per 24 h over a period of 1 week. This was done before start of the diet and repeated in week 6 and week 12 (Fig. 1).

The PAL was used together with the WHO resting energy equation [14] to calculate the Total Energy Expenditure (TEE) for diet customization [15].

2.2.4. Questionnaires

Questionnaires were administered before start of the diet and repeated in week 4 and at the end visit (Fig. 1). The Twelve Item Short Form Survey (SF12), a practical, reliable and valid measure of physical and mental health [16], was used to measure functional health and quality of life. The Checklist Individual Strength (CIS) is a 20-item, questionnaire that captures different domains of fatigue. Furthermore, a questionnaire was composed to examine the burden of the diet, headache and gastrointestinal complaints. Questions on frequency and severity of gastrointestinal complaints (nausea, vomiting, burping, postprandial fullness, bloating, loss of appetite, flatulence, constipation, diarrhea and dysphagia) were selected from a validated Dutch gastrointestinal questionnaire [17], which has been used previously in this patient group [18].

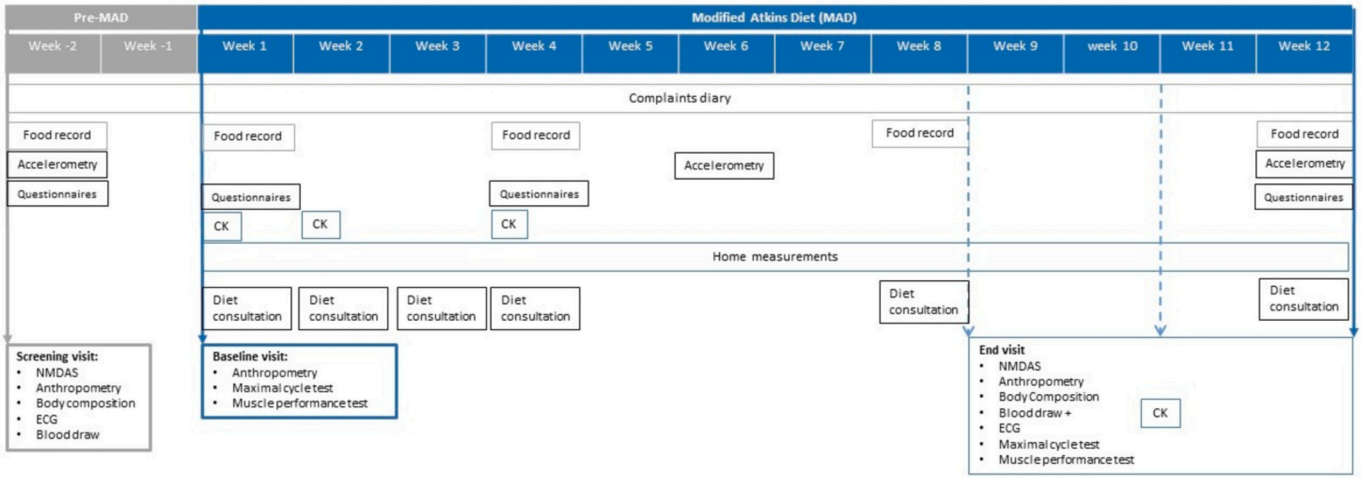

Fig. 1. Study schedule.

2.2.5. Creatine kinase (CK)

CK was determined during the study visits and at a laboratory in the hometown during the first weeks of the intervention (Fig. 1) as a marker of muscle damage. A CK between 1000 and 5000 μ/l was indicated as mild rhabdomyolysis and a CK of 5000 μ/l or more was indicated as severe rhabdomyolysis in this study [19]. In presence of severe muscle pain (NRS ≥8) in the complaint diary, extra CK checks were performed.

2.2.6. Home measurements

Ketone (Beta hydroxybutyrate) and glucose levels were measured at home with a portable tester (StatStrip Xpress®). Ketones were measured three times a week during the first four weeks of MAD and once a week thenceforth. Glucose levels were measured 3 times per week during the first week of the intervention and when hypoglycemia symptoms occurred. Weight was measured once a week.

2.2.7. Newcastle Mitochondrial Disease Scale for Adults (NMDAS)

The NMDAS is a semiquantitative clinical rating scale, designed specifically for all forms of mitochondrial disease, to monitor disease severity [20]. The NMDAS was performed at screening and at the end of the intervention period. The NMDAS scale considers many parameters, including myopathy, diabetes, gastrointestinal complaints and cardiac involvement.

2.2.8. Maximal incremental test

A maximal incremental test was performed at baseline and at the end of the intervention period on a cycle ergometer (Lode Excalibur, Groningen, the Netherlands). An electrocardiogram (ECG) was performed prior to the maximal incremental test to determine whether the maximal incremental cycling test could be performed safely. O_2 and CO_2 partial pressures were continuously sampled by a mass spectrometer (Quark CPET, COSMED, Rome, Italy), which was calibrated before every test by both ambient air and a fixed known gas mixture [21]. Heart rate (HR) was measured continuously by ECG, blood pressure was assessed every 3 min, and lactate was determined at rest, before the start of the test and immediately at its end. The ramp protocol started at a workload of 10 W and increased gradually with 10 W/min until exhaustion. Patients were instructed to maintain a cadence between 60 and 80 rpm during the test. All participants were verbally encouraged throughout the maximal incremental test to reach maximum.VO_2 peak was defined as the highest 30-s VO_2 average reached during the exercise protocol (ml/min), and consequently adjusted for body weight (ml/kg•min) [21]. The anaerobic threshold (AT) was determined using the V-slope method [22] and consequently presented as percentage of the absolute VO_2 peak.

2.2.9. Muscle performance test

Electrically stimulated, isometric quadriceps muscle contractions were obtained to determine resistance to fatigue at baseline and the end of the dietary intervention as previously described [23]. Briefly, Maximal Voluntary Contraction (MVC) of the quadriceps muscle of the dominant leg was assessed and subsequently involuntary muscle contractions were induced at 40 % of the MVC to assess fatigue resistance by repetitively using 30 Hz bursts of 1 s duration every 2 s (on to off time ratio, 1 s:1 s) for 2 min. Muscle fatigue resistance was analyzed by measuring the percent decline in muscle force over the stimulation protocol.

2.2.10. Anthropometry

Weight (kg), height (cm) and waist circumference (cm) were measured with Seca® devices during the study visits.

2.2.11. Body composition

Body composition was determined at the screening and after intervention period with single frequency bioimpedance analysis (SF BIA) (Bodystad 1500 MDD®). Fat free mass (kg) and fat percentage were calculated using the formula of Kyle [24].

2.2.12. Blood samples

Blood samples were collected at screening and at the end of the intervention period after an overnight fast to determine lipid profile (triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol), uric acid, ALAT, Bicarbonate, lactate, (fasting) glucose, natrium and potassium. All analyses were done in the clinical laboratory of the Radboudumc.

2.3. Safety protocol

Adverse events (AEs) were the primary outcome variables for safety. Predefined severe AEs included 1) Malnutrition: body mass index (BMI) declines below 18.5 kg/m^2 or weight loss of more than 10 % of pre-intervention body weight in non-obese patients.

2) Mild rhabdomyolysis: CK level > 1000 μ/l. 3) Muscle pain: three point increase on the NRS scale for muscle pain or a score above eight. 4) Vomiting: recurrent vomiting.

2.4. Dietary intervention

During MAD, carbohydrate intake was limited to a maximum of twenty grams per day and the intake of fat rich products was encouraged. The diet was personalized based on food preferences, intolerances, and TEE. Patients had to gradually restrict carbohydrate intake in the first week, after which the diet was further adapted based on individual preferences, ketone levels and complaints. Supplements containing Medium Chain Triglycerides (MCTs) were provided if ketone levels stayed below 1 mM, laxatives were prescribed in case of obstipation, and patients were encouraged to drink sufficient amount of water to prevent dehydration.

Diet consultation took place during the baseline visit and by video or telephone weekly during the first 4 weeks of diet intervention (Fig. 1). During these consultations, patients received instructions on implementation and finetuning the diet.

2.5. Data analysis

All data were collected in an online database (Castor®). Statistical tests were performed using SPSS statistics (IBM, version 25). Normal distribution was checked by the Shapiro Wilk test. Continuous normally distributed data were presented as mean ± standard deviation (SD), continuous not normally distributed data as median and interquartile range (IQR), and categorical variables as percentage. Differences in continuous variables between baseline and the end of MAD were checked using the Paired *t*-test (normal distribution) and Wilcoxon Signed Rank test (non-normal distribution).

3. Results

3.1. Patient characteristics

Medical files of 515 MD patients at the Radboudumc were screened based on in and exclusion criteria, resulting in 54 eligible patients, of which 26 showed interest to participate. Three patients were excluded after the screening visit based on exclusion criteria and three other patients retracted from participating (Fig. 2). Twenty patients (seventeen females and three males) took part in the study.

Most patients (n = 15) had a mtDNA point mutations, the m.3243A>G mutation was the most frequently present genotype (n = 5). Five patients had mtDNA deletions and two of those had one or more additional nuclear DNA mutations.(Table 2). Patients were 46 ± 13 year old and had a BMI of 24 ± 4 kg/m^2 (Table 1).Mean NMDAS was 19 ± 8 and eleven patients had a severe disease burden (>20) according to the NMDAS (Table 2). All patients had a myopathic phenotype as this was an inclusion criterion but the myopathy was generally mild since they had to be able to perform the muscle performance test. None of the patients

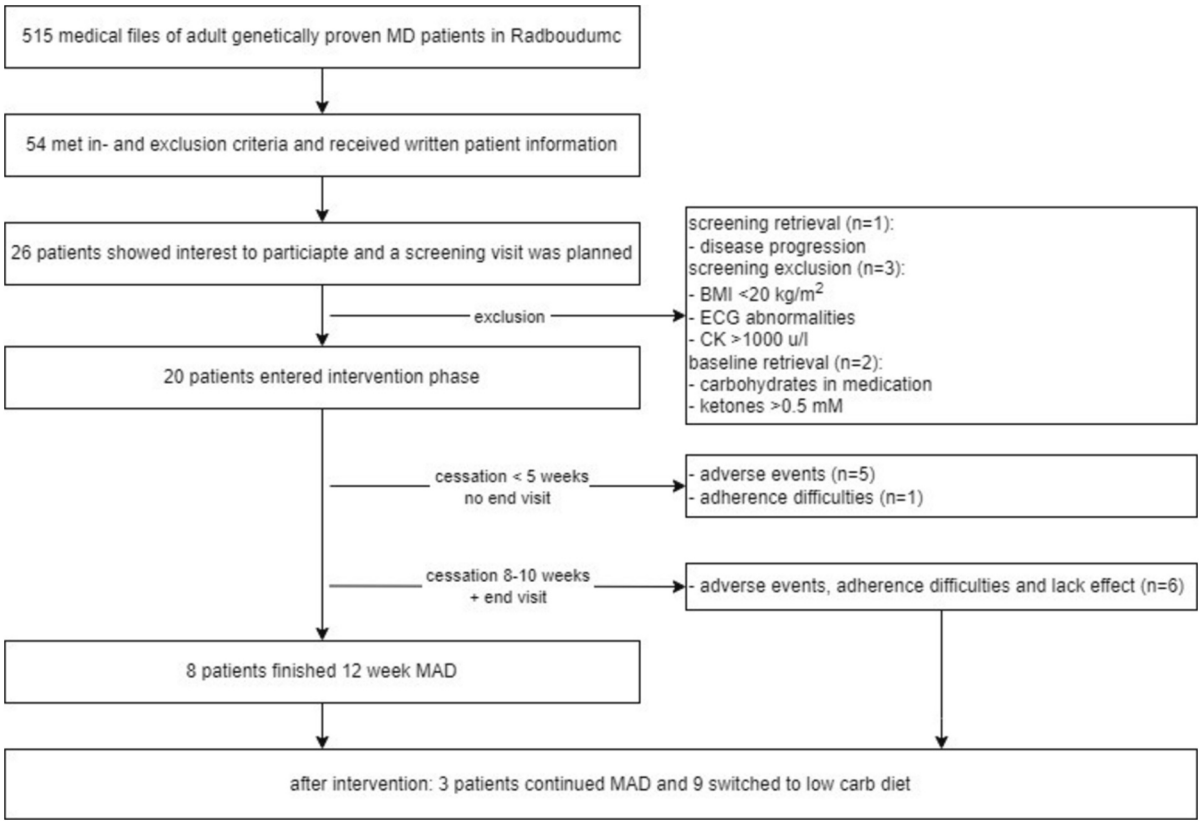

Fig. 2. Flowchart of patient inclusion.

were wheelchair dependent or had tube feeding. Epilepsy, strokes or encephalopathy was not present in this cohort. Ataxia was more common ($n = 14$) and mild neuropathy was present in 7 patients. Cognition of the patients was not impaired.

3.2. Feasibility

Eight out of twenty patients completed the twelve week MAD intervention (Fig. 1). During the first four weeks of MAD, six patients stopped the diet without an end visit, due to difficulties with dietary adherence ($n = 1$) or adverse events ($n = 5$), including rhabdomyolysis ($n = 3$), vomiting (n = 1) and self-reported exercise intolerance ($n = 1$). Six other patients stopped the diet after eight to ten weeks, followed by an end visit, due to difficulties with dietary adherence, a subjective lack of effect, in combination with adverse events: such as exercise intolerance/fatigue ($n = 5$), or obstipation ($n = 1$). From the patients with a mtDNA deletion ($n = 5$) or a MERFF mutation($n = 4$), only one patient finished the study. The five patients with the m.3243A>G mutation were able to achieve the longest diet duration (Table 2). Almost all patients who followed MAD were able to achieve ketosis ($n = 19/20$) (Table 1). The majority of patients maintained ketone levels between 0.5 and 1.5 mmol/l, and two patients above 2.0 mmol/l. Three patients failed to stay in ketosis (Table 2).

3.3. Safety

No serious adverse events occurred during the study; no hospital admissions occurred and no participant died. Safety issues that arose in three patients were the occurrence of severe rhabdomyolysis (CK = 6789 U/l) accompanied by muscle pain (NRS = 8/10) ($n = 1$), and mild rhabdomyolysis (CK = 1072; 1003 μ/l) with muscle pain (NRS = 8/10; 3/10) ($n = 2$) (Fig. 1).The three patients who developed rhabdomyolysis have genotypes in which ragged red fibers (RRF) can be present (mtDNA deletions ($n = 2$) and the m.8363G>A mutation ($n = 1$), unfortunately muscle biopsies were unavailable (Table 2). None of the other patients who had RRF precent in their muscle biopsies ($n = 4$), developed CK elevations (Table 2). After discontinuation of MAD, CK levels dropped again within one week (<1000 μ/l). Other adverse events that caused cessation of the MAD were vomiting ($n = 1$), exercise intolerance/fatigue ($n = 6$) and obstipation ($n = 1$).

Furthermore, AEs were mentioned in complaint diaries. Some of these AEs, such as fatigue, muscle complaints and gastrointestinal complaints, became worse during the first four weeks of MAD, but decreased again in the weeks that followed. Headache slowly became less prevalent over time (Fig. 3A). No patients experienced dyslipidemia, hypoglycemia or lactate elevations.

3.4. Efficacy

End tests were performed in fourteen participants at eight ($n = 5$), ten ($n = 1$) or twelve ($n = 8$) weeks of the dietary intervention (Table2 and Fig. 2). Data from eleven patients was available for analyses of the maximal incremental exercise test. Data from three patients were missing due to exercise intolerance ($n = 1$) and equipment failure ($n = 2$) (Table2). Out of these eleven patients, six patients showed a (4–31 %) increase in VO_2peak (ml/kg•min) and three of those also increased the absolute VO_2peak 4–23 % (ml/min) (Table 2, Fig. 4A, and Supplementary table 1). Nine increased their AT as percentage of VO_2-peak (3–83 %) after the dietary intervention (Table 2, Fig. 4B and Supplementary table 1). Overall, MAD did not improve the maximal exercise performance. Pre-exercise and post-exercise lactate levels decreased after the MAD intervention for 10/11 and 9/11 patients respectively (Table 1).

On a group level muscle performance remained similar after the MAD. Of the 14 patients tested at the end of the intervention, half showed higher MVC after MAD (Tabel 2 and Fig. 4C). The fatigue resistance protocol could not be completed in three patients at the end of

Table 1
Feasibility and safety outcomes before Diet (pre MAD) and after Modified Atkins Diet (End MAD).

	Pre MAD (total)	*N*	Pre MAD (with end)	E nd MAD	*N*	P-value
Feasibility						
Nutritional intake						
Energy (kcal/day)	1661 ± 401	17	1768 ± 386	1608 ±451	12	0.41
Protein (g/day)	70 ± 15	17	72 ± 17	91 ± 20	12	0.02
Carbohydrate (g/day)	159 [71]	17	176 [66]	17 [49]	12	<0.01
Fat (g/day)	75 ± 26	17	81 ± 27	127 ± 46	12	0.01
MCT (g/day)	0 ± 0	16	0 ± 0	10 ± 15	12	0.05
Beta-hydroxybutyrate (mmol/L)	0.15 ± 0.11	19	0.14 ± 0.08	0.98 ± 0.72	12	<0.01
Safety						
Anthropometry						
Body mass (kg)	68.6 [14.1]	20	68.1 [14.7]	67.5 [13.0]	14	0.02
Waist circumference (cm)	92 ± 12	20	92 ± 14	89 ± 13	14	0.14
Body composition						
BMI (kg/m^2)	24.2 [4.3]	20	23.9 [7.7]	23.6 [6.2]	14	0.02
FFMI (kg/m^2)	14.4 [2.8]	20	14.3 [1.9]	13.9 [3.2]	14	0.09
Fat (%)	40 ± 7	20	41 ± 6	40 ± 7	14	0.42
Blood						
Fasting glucose (mmol/l)	5.6 [0.6]	20	5.6 [0.7]	5.1 [0.8]	14	0.16
Cholesterol (mmol/l)	5.1 ± 0.7	20	5.2 ± 0.8	5.1 ± 0.8	14	0.69
HDL (mmol/l)	1.4 [0.6]	20	1.4 [0.6]	1.7 [0.6]	14	0.05
LDL (mmol/l)	3.0 ± 0.6	19	3.1 ± 0.5	3.2 ± 0.8	13	0.62
TG (mmol/l)	1.0 [1.1]	20	1.1 [1.1]	0.8 [0.1]	14	<0.01
Pre-exercise lactate (mmol/l)	2.6 ± 1.2	19	3.0 (1.4	1.9 ± 0.7	10	<0.01
Post-exercise lactate (mmol/l)	8.4 ± 2.2	19	9.2 ± 2.2	7.7 ± 2.6	10	0.0 5
Delta lactate (mmol/l)	5.8 ± 1.0	19	7.2 ± 0.8	5.8 ± 1.9	10	0.97

Data are presented as mean ± SD or median [IQR]. Number of patients included in results per test result is specified by *N*.; BMI: body mass index; FFMI: fat free mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; MCT: medium chain triglycerides.

the intervention due to experienced pain during the baseline test. On average, fatigue resistance was unaffected by the MAD, but improved in 5 out of 11 patients (Tabel 2 and Fig. 4D).

Body weight, BMI, HDL cholesterol, and triglyceride levels decreased by the dietary intervention (Table 1). For the other efficacy outcomes, overall, no significant effect was found. Glucose tolerance increased in 7/14 patients (Table 2).

NMDAS increased in 6/14 patients (Table 2).In total, 10/14 patients who followed MAD for at least eight weeks, reported positive effects of the diet, such as decreased feelings of fatigue, increased muscle performance, headache reduction and reduction of gastrointestinal symptoms (Fig. 2B). Furthermore, thirteen patients lost weight during the dietary intervention which was reported to be a negative effect of the dietary intervention in one patient.

4. Discussion

Due to the absence of a curative treatment, it is of major importance to examine nutritional interventions that might reduce symptoms in patients with MD. Since only a few studies have examined a ketogenic diet in this patient group, this study aimed to increase understanding on the feasibility, safety and efficacy of MAD in MD.

MAD is feasible for most MD patients for a short period of time (±4 weeks), since almost all patients reached ketosis and carbohydrate intake was below the instructed quantity. However, only 40 % of patients fulfilled the twelve week program. Ketone levels at the end visit were low and many patients reported difficulties with dietary adherence, and only three patients continued the diet after the intervention period due to positive effect. This suggests that MAD is less feasible for a large group of patients on the long-term. This is in line with previous reports on KD in children with epilepsy [25].

An important safety issue of MAD that arose in three patients was the occurrence of (mild) rhabdomyolysis. In the study of Ahola et al., the occurrence of rhabdomyolysis was reported during MAD in all five of the participating CPEO patients. It was suggested that ragged red muscle fibers (RRF) played a role [10]. In the current study some but not all MM patients with CPEO or RRF in muscle biopsy develop rhabdomyolysis when following MAD. A recent study in 33 children with MD, including some forms that are likely to have RRF, on KD also did not report any rhabdomyolysis [11]. A follow-up study of Ahola et al., showed an increased muscle strength in all patients who developed muscle damage, 2.5 years after the dietary intervention [10]. This may point towards a replacement of the necrotic muscle fibers by healthy cells, via satellite cell fusion, in the recovery phase [4]. Taken together, rhabdomyolysis is a potential risk of MAD in MD patients. Therefore, CK levels and muscle symptoms should be monitored closely when initiating a KD, especially in the first weeks.

Gastrointestinal symptoms were commonly reported, which is in line with literature [18]. Occurrence increased in the first four weeks, after which they decreased again. This could possibly be explained by the provision of laxatives in patients reporting obstipation, or by the transient nature of side effects correlated with the diet, often described as keto adaptation [26,27]. Noteworthy, gastrointestinal symptoms were no reason for dropout in most patients, suggesting it might be an tolerable side effect. Moreover, MAD also improved gastrointestinal symptoms in some patients. For two patients, these improvements were life changing in such way, they decided to continue the diet despite adverse events. A probable explanation for these changes in gastrointestinal symptoms could be alterations in the gut microbiome induced by MAD [28].

There was a significant reduction in weight and BMI on a group level. Since MD patients are at risk to develop malnutrition, and KD is known to cause weight loss, signs of malnutrition were monitored closely during the study [29]. However, weight loss was considered a desirable effect in most patients. Therefore, MAD could be a suitable treatment option for overweight and obese MD patients to achieve optimal weight and body fat percentage [30].

On a group level no conclusions on efficacy can be drawn because only a few patients completed the study and ketone levels at the end visit were mostly below the expected therapeutic level.

The outcome of the maximal incremental test showed variation in individual response during MAD. The observed trend towards increased AT upon MAD could indicate an increased capacity to utilize fats before switching to anaerobic energy supply. This was also reflected in lower levels of lactate in rest and after exercise. Since lactate accumulation is known to negatively influence endurance performance and muscle fatigue [31], a decrease could potentially benefit physical performance. Taken together, MAD could be beneficial to improve exercise performance in a subset of MD patients but more studies with a longer duration are necessary to draw conclusions on this subject.

The effect of MAD on the maximal voluntary contractile force and

Table 2
Individual baseline characteristics, diet characteristics and efficacy results.

Baseline characteristics						Diet characteristics					Efficacy MAD							
Sex	Genotype	Phenotype	NMDAS	Hetreo-plasmy %	RRF	diet duration	reason to stop MAD	Mean Ketone level	Ketone levels during end tests	Diet after study	Δ VO_2peak ml/kg/min(%)	AT.% Δ	Δ Fatigue resistance (*N*,%)	Δ MVC (*N*, (%))	Δ Cis fatigue	Δ NMDAS	Δ fasting glucose	Weight loss (%)
F	mtDNA del	CPEO	35	40 (O)	NA	3 days	Severe Rhabdomyolysis	0.9	NA	none	NA	NA	NA	NA	NA	NA	NA	NA
M	m.8344A>G	MERFF	17	28 (U)	NA	<3 weeks	Adherence problems	NA	NA	none	NA	NA	NA	NA	NA	NA	NA	NA
F	m.8363G>A	MERFF	28	41 (M)	NA	3 weeks	mild Rhabdomyolysis	NA	NA	none	NA	NA	NA	NA	NA	NA	NA	NA
F	m.7472insC	MM	26	NA	NA	26 days	vomiting	0.8	NA	none	NA	NA	NA	NA	NA	NA	NA	NA
F	m.14484T>C	LHON	20	NA	NA	<4 weeks	exercise intolerance	1.8	NA	LCD	NA	NA	NA	NA	NA	NA	NA	NA
M	nDNA C10ORF2 (TWINKLE) c.1925A>G heterozygote + del mtDNA	CPEO	25	NA	NA	5 weeks	mild Rhabdomyolysis	1.2	NA	none	NA	NA	NA	NA	NA	NA	NA	NA
F	m.8363G>A	MERFF	17	39 (U)	yes	8 weeks	Fatigue, exercise intolerance, no positive effect	0.7	0.5	LCD	**0.9 (5 %)**	**11 (19 %)**	**6 (19 %)**	**30 (8 %)**	NA	6	0.5	**3.1**
F	m.8363G>A	MERFF	32	NA	NA	8 weeks	Fatigue, exercise intolerance, difficult diet, no positive effect	1.0	0.4	LCD	**0.8 (5 %)**	**1.8 (2 %)**	**3 (9 %)**	−46 (−13 %)	−13 (−16 %)	2	**−0.4**	**6.6**
F	nDNA DNA2 c.2286T>G (heterozygote) and RRM1 c.1141C>T (homozygote) + del mtDNA	CPEO	21	NA	yes	8 weeks	Fatigue, less energy, no positive effect	1.4	1.6	LCD	−1.8 (−13 %)	**25.5 (53 %)**	−7 (−22 %)	−16 (−5 %)	NA	4	**−0.4**	−0.4
F	m7472insC	MM	10	95 (M)	no	8 weeks	Fatigue, no positive effect	0.4	0.2	none	−0.1 (−1 %)	−7.1 (−9 %)	NA	**8 (2 %)**	**11 (22 %)**	**−2**	0.1	−0,5
F	mtDNA del	CPEO	23	50 (M)	yes	8 weeks	Obstipation, no effect on energy and difficult diet	1.0	1.3	none	NA (EF)	NA (EF)	**2 (9)**	−48 (−15 %)	NA	**−1**	0.1	**2.2**
F	m.3243A>G	MM	21	13 (U)	no	10 weeks	Fatigue, no positive effect and difficult diet	0.5	0.4	none	−0.1 (−0 %)	**1.30 (3 %)**	NA	**107 (39 %)**	**9 (10 %)**	4	0.6	**1.1**
F	m.9176T>C	MM	24	99 (B)	NA	12 weeks	NA	0.7	0.7	LCD	NA (EF)	NA (EF)	**13 (39 %)**	**216 (71 %)**	NA	**−4**	0	**5.8**
F	m.3243A>G	MM	8	83 (U)	NA	12 weeks	NA	2.4	2.2	LCD	**4.2 (19 %)**	**13.5 (25 %)**	−11 (−22 %)	−125 (−15 %)	**2 (3 %)**	**−4**	**−0.4**	**14**
F	m.3243A>G	MM	11	50 (U)	NA	12 weeks	NA	2.4	2.5	LCD	**3.4 (14 %)**	**8.8 (16 %)**	−13 (−33 %)	**28 (5 %)**	**11 (15 %)**	**−1**	**−0.8**	**2.3**

(*continued on next page*)

Table 2 (*continued*)

Baseline characteristics						Diet characteristics				Efficacy MAD							
Sex	Genotype	Phenotype	NMDAS	Hetreo-plasmy %	RRF	diet duration	reason to stop MAD	Mean Ketone level	Ketone levels during end tests	Diet after study	Δ VO_2peak ml/kg/min(%)	Δ AT.% Δ	Δ Fatigue resistance (N,%)	Δ MVC (N, (%))	Δ Cis fatigue	Δ NMDAS	Δ fasting glucose	Δ Weight loss (%)
F	m.3243A>G	MM	13	83 (U)	NA	12 weeks	NA	1.0	0.8	LCD	**1 (4 %)**	**4.3 (7 %)**	−9 (−20 %)	−20 (−4 %)	NA	3	**−0.4**	**9.1**
F	mtDNA del	CPEO	25	65 (M)	no	12 weeks	NA	1.5	1.3	LCD/ FODMAP	NA (AE)	NA (AE)	−4 (−15 %)	−73 (−19 %)	NA	2	0.3	**5.8**
F	m7472insC	MM	8	NA	yes	12 weeks	NA	0.9	1.3	MAD/ LCD	**5.9 (31 %)**	**30.3 (83 %)**	NA	−1 (−0 %)	−72 (−240 %)	0	**−0.6**	5.9
F	m.9176T>C	Leigh	15	89 (U)	NA	12 weeks	NA	0.8	0.4	MAD/ LCD	−1.9 (−8 %)	**1.5 (3 %)**	−3 (−9 %)	**10 (4 %)**	**13 (20 %)**	1	0.1	−0.6
F	m.3243A>G	MM	7	32 (U)	NA	12 weeks	NA	1.8	1.0	MAD	−2.5 (−9 %)	−3.5 (−7 %)	**19 (140 %)**	**62 (15 %)**	**28 (32 %)**	**−1**	**−0.6**	**8.2**

Abbreviations: CPEO: chronic progressive external ophthalmoplegia; Del: deletion; F: female; FODMAP: Fermentable oligosaccharides, disaccharides, monosaccharides and polyols; ins: insertion; Ketone levels: Beta hydroxybutyrate (mmol/L); LCD: low carbohydrate diet; LHON: Leber Hereditary Optic Neuropathy; M: male; MERFF: myoclonic epilepsy with ragged red fibers; MFR: Muscle fatigue resistance; MM: mitochondrial myopathy; mtDNA: mitochondrial DNA; NA: not applicable; nDNA: nuclear DNA; RRF: Ragged red fibers; RRM1: ribonucleotide reductase catalytic subunit M1; M = muscle tissue; U = urine; O = other; Clinical relevance indicated as: Improvement; EF: equipment failure; AE: adverse events. **Bold**= improvement

resistance to fatigue was shown to be variable per individual. However, improvement in maximal incremental cycle performance did not seem to be associated with more fatigue resistance or peak muscle performance. Therefore, suggesting different mechanisms to be important for these performance types.

Fatigue was a frequently reported symptom in our study. Occurrence fluctuated over time, and both increase and decrease of symptoms was reported upon MAD. Fluctuations could possibly be explained by the keto adaptation phase [26,27]. Increased fatigue symptoms could be caused by an increase in muscle fatigue following KD [32] or the implementation of the new strict diet. Decreased fatigue could rely on an improved mitochondrial energy metabolism in some individuals [33]. However, since fatigue is a common feature of MD, and no control group was included, results could not be compared to normal fluctuations of the disease. In addition, the etiology of fatigue is still poorly understood, making it a difficult concept to grasp in general. Therefore, despite the fact that we examined fatigue from multiple angles, drawing clear conclusions on the effect of MAD remains challenging.

Several secondary efficacy outcomes showed improvements. In line with literature, reduced headache and migraine were reported [34,35]. Earlier research suggested that using a high fat diet, an unfavorable lipid profile might occur [7]. In the present study, we found an improved lipid profile, containing significantly lower triglycerides and higher levels of HDL cholesterol. We excluded patients with dyslipidemia, so we can't say if this positive effect on the lipid profile would apply to these patients as well. Furthermore, glucose tolerance improved in half of patients. Both of these findings were comparable with a previous study in diabetes mellitus (DM) type 2 patients and obese patients on KD[36,37] [38] [39]. These changes could be caused directly by low carbohydrate intake, indirectly via weight loss or mediated by alterations in the gut microbiome [40,41,42,38].

Safety and efficacy of MAD were highly variable among patients with different mutation types. Patients with a mtDNA deletion or a MERFF mutation, all experienced muscle related adverse events and only one patient finished the study but with major muscle symptoms. The five patients with the m.3243A>G mutation experienced less side effects and were able to achieve the longest diet duration. Improvements on glucose tolerance are particularly relevant in this subgroup, since maternally inherited diabetes and deafness (MIDD) is its most frequently reported phenotype. Other studies also mentioned good response to KD in this subgroup [43,11].

Strengths of this study include the fact that patients were investigated in a systematic way, patients were monitored and guided closely, and validated measurement methods were used. The small sample size, the heterogeneous patient group, the absence of a control group, binding of the intervention and control intervention and the sex imbalance are limitations.

To conclude, MAD is feasible for a short period of time in a proportion of MD patients, but adherence might be difficult on the long run. The diet is safe for a subset of the patients, but not all. Efficacy seems to be highly variable between patients. Several benefits were shown on an individual level (not reaching statistical significance) in different domains, such as muscle strength, exercise performance, glucose tolerance and body weight. Possible indications to try MAD in MD could include glucose intolerance, gastrointestinal symptoms, migraine, obesity and the m3243A>G mutation. MAD appears to be unsuitable for MD patients with mtDNA deletions and MERFF mutations. All patients should be supervised and monitored closely for adverse events when initiating the diet. Further research should focus on predictive factors to consider the diet, effectiveness of less stringent carbohydrate restricted diets and the relation of MAD and the microbiome in MD patients. These future studies should include: controlled studies, single genetic diagnosis studies and larger scale studies.

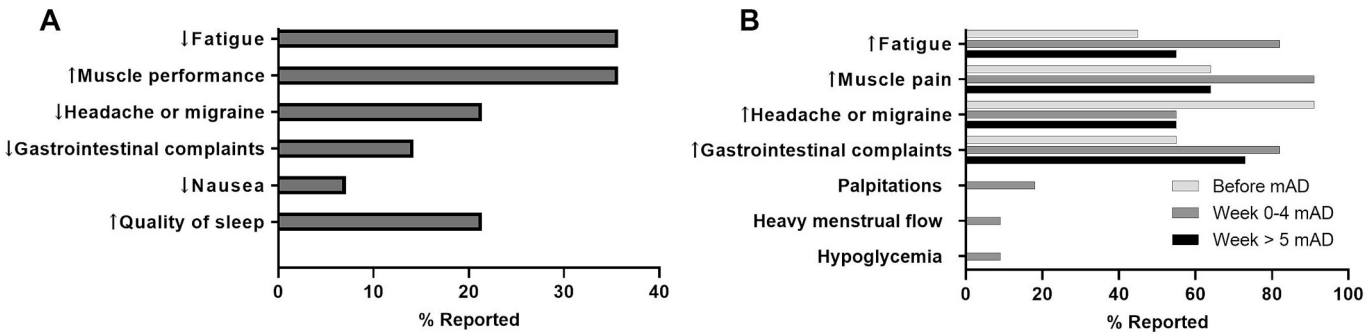

Fig. 3. Subjective effects of modified Atkins Diet (mAD) mentioned in the complaints diary and questionnaire. (A) Positive effects: throughout the study ($n = 14$) (%). (B)Negative effects: before mAD, week 0–4 mAD, week ≥5 mAD (%);↑ = increase, ↓ = decrease ($n = 11$).

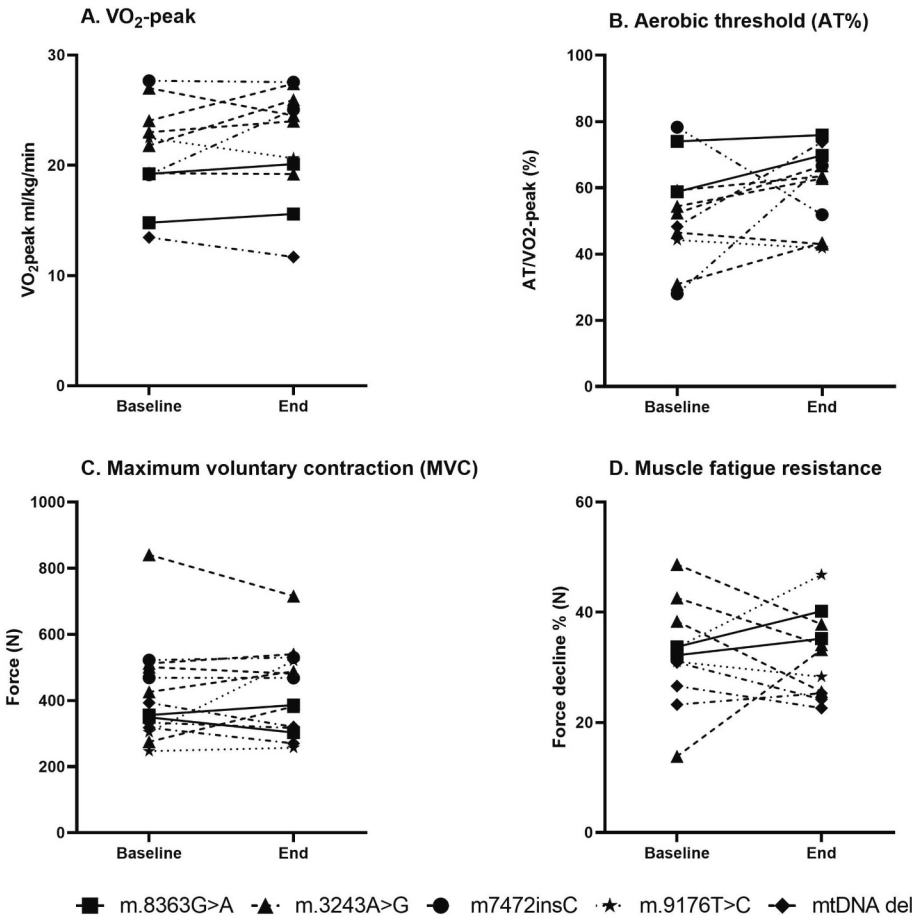

Fig. 4. Efficacy effects in myopathy measured by maximal incremental cycle test and muscle performance test (A) VO_2peak performance during the maximal incremental cycle test. Every line represents a patient per genotype (B) AT value as a percentage of VO_2 peak. (C) Absolute force response during voluntary contraction (D) Fatigue resistance is expressed as a percentage of pre fatigue value.

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CRediT authorship contribution statement

Heidi E.E. Zweers: Writing – original draft, Investigation, Conceptualization. **Sophie H. Kroesen:** Writing – review & editing, Writing – original draft, Formal analysis. **Gijsje Beerlink:** Writing – original draft, Formal analysis. **Elke Buit:** Writing – review & editing. **Karlijn Gerrits:** Writing – review & editing. **Astrid Dorhout:** Writing – review & editing. **Annemiek M.J. van Wegberg:** Writing – review & editing. **Mirian C.H. Janssen:** Writing – review & editing, Conceptualization. **Saskia B. Wortmann:** Writing – review & editing. **Silvie Timmers:** Writing – review & editing, Methodology. **Christiaan G.J. Saris:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

SW and HZ received a travel grants From Nutricia.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2024.108610.

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