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SUBSTRATE OXIDATION & CARDIAC PERFORMANCE DURING EXERCISE IN DISORDERS OF LONG CHAIN FATTY ACID OXIDATION

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Abstract

Background—The use of long-chain fatty acids (LCFAs) for energy is inhibited in inherited disorders of long-chain fatty acid oxidation (FAO). Increased energy demands during exercise can lead to cardiomyopathy and rhabdomyolysis. Medium-chain triglycerides (MCTs) bypass the block in long-chain FAO and may provide an alternative energy substrate to exercising muscle.

Objectives—To determine the influence of isocaloric MCT versus carbohydrate (CHO) supplementation prior to exercise on substrate oxidation and cardiac workload in participants with carnitine palmitoyltransferase 2 (CPT2), very long-chain acyl-CoA dehydrogenase (VLCAD) and long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) deficiencies.

Design—Eleven subjects completed two 45-minute, moderate intensity, treadmill exercise studies in a randomized crossover design. An isocaloric oral dose of CHO or MCT-oil was administered prior to exercise; hemodynamic and metabolic indices were assessed during exertion.

Results—When exercise was pretreated with MCT, respiratory exchange ratio (RER), steady state heart rate and generation of glycolytic intermediates significantly decreased while circulating ketone bodies significantly increased.

Conclusions—MCT supplementation prior to exercise increases the oxidation of medium chain fats, decreases the oxidation of glucose and acutely lowers cardiac workload during exercise for the same amount of work performed when compared with CHO pre-supplementation. We propose

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that MCT may expand the usable energy supply, particularly in the form of ketone bodies, and improve the oxidative capacity of the heart in this population.

INTRODUCTION

Long-chain fatty acid oxidation (FAO) disorders are the result of recessively inherited deficiencies of enzymes in the mitochondrial fatty acid β-oxidation pathway. Subjects with long-chain FAO disorders often have recurrent episodes of rhabdomyolysis with elevated creatine kinase levels and chronic exercise intolerance[1–3]. Thus, patients are typically counseled on the potential risks of exercise and often adopt a relatively sedentary lifestyle.

Previous research has suggested that medium chain triglyceride (MCT) supplementation administered prior to exercise improves exercise tolerance in individuals with long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) deficiency. A decrease in steady-state heart rate (HR) has also been observed in participants supplemented with MCT oil prior to exercise, suggesting a cardiac benefit [4]. Changes in heart rate are noteworthy due to an increased incidence of cardiomyopathy among patients with long-chain fatty acid oxidation disorders [5–7]. MCT bypasses the block in long-chain fatty acid (LCFA) oxidation and may provide a usable source of fatty acids for both the heart and exercising skeletal muscle. In a previous study, no significant difference in respiratory exchange ratio (RER) was observed when orange juice + MCT versus orange juice alone were administered prior to exercise [4], however these supplements were not isocaloric. Only subjects with LCHADD were included in this initial study; subjects with other long-chain FAO disorders that affect exercise tolerance may also benefit from a pre-exercise MCT supplement. The aims of the present study were to determine the effect of isocaloric MCT vs. CHO supplementation prior to exercise on substrate oxidation and cardiac function during submaximal exercise in subjects with a variety of long-chain FAO disorders. We hypothesized that subjects with different long-chain FAO disorders would respond to pre-exercise MCT supplementation in a similar manner.

METHODS

Recruitment

Subjects were recruited from previous studies and by physician referral. The first subject to enroll in this study began in 2007; in 2010, the last subject completed the trial. The inclusion criteria involved a confirmed diagnosis of a long-chain fatty acid oxidation disorder including very long-chain acyl-CoA dehydrogenase (VLCAD; OMIM # 201475), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD; OMIM #609016), mitochondrial trifunctional protein (TFP; OMIM #609015) or carnitine palmitoyltransferase-2 (CPT2; OMIM #255110) deficiency, seven years of age or older and the ability to comply with the study protocol. The study was approved by the OHSU Institutional Review Board (OHSU eIRB 817, www.clinicaltrials.gov NCT00654004). Subjects over 18 years of age gave written informed consent to participate. Each participant under 18 years of age provided written assent in addition to written informed consent from a legal guardian.

Study design

Each subject completed the treadmill exercise test twice, at baseline and 4 months, in a randomized crossover design. Subjects were admitted to the inpatient research unit at OHSU for 3 nights per visit. A random sequence allocation was used to determine the order in which the pre-exercise supplement was administered.

Pre-Exercise Supplement & Dual-energy X-ray Absorptiometry (DEXA)

Lean body mass (LBM) in kilograms was determined by DEXA prior to treadmill testing. MCT, (8 kcals/gm), was administered prior to exercise testing relative to LBM at 0.5g MCT/kg LBM, and was then added to approximately 12 ounces of a calorie-free beverage. For the CHO (4 kcals/gm) supplemented exercise test, subjects consumed a full calorie juice or soda beverage at 1 gm CHO /kg LBM to achieve isocaloric supplementation.

Exercise Testing

Patients began treadmill ergometry 2 hours after a standardized low-fat lunch that provided approximately 25% of estimated total energy requirements. Randomized supplementation was administered 20 minutes prior to exercise. Four months later, subjects received the alternate beverage supplement and repeated treadmill ergometry at the same grade, speed and duration as the first test to keep work performed constant between trials.

Treadmill testing was performed on an SMC 2000 treadmill (Sensor Medics, Yorba Linda, CA) with continuous ECG monitoring using a Sensor Medics Cardiosoft digital system. Respiratory gases were collected using a mouthpiece or Hans-Rudolph mask and gas exchange was measured using a Sensor Medics VMAX 29 metabolic cart.

The exercise protocol was performed as follows: 3 minute warm up phase with a slow walk at 1.5 miles per hour at 0% grade followed by increases in rate and incline every 2 minutes until the subject's heart rate achieved 60–70% of his/her predicted maximum heart rate. Subjects were asked to continue exercising at 60–70% of their predicted maximum heart rate for an additional 40 minutes after the warm up phase. Predicted maximum heart rate was calculated using the formula: 220 (beats per minute) – age in years. A 12-lead ECG was placed prior to exercise for the continual monitoring of the electrical activity and rate (bpm) of the heart during exercise. Using a blood pressure cuff, blood pressure (BP) data was also collected during exercise at least one time during the first 20 minutes and last 20 minutes of the test. Gas exchange was measured continuously. However, in some cases gas exchange was collected just during the first 15 minutes and the last 15 minutes of exercise, giving the subject a period of rest from wearing the collection apparatus. Heart rate, VO_2 (mL/kg/min) & RER were recorded at one-minute intervals. Myocardial O_2 consumption during exercise was estimated using a double product calculation, (systolic BP×HR), an indirect measure of ejection fraction (EF).

Blood Samples

An indwelling catheter was placed for repeated blood collection. Eight ml blood samples were drawn at pre-exercise (0 min), post-exercise (40 min), and recovery (60 min) time-points. Tetrahydrolipostatin was added to EDTA plasma to inhibit lipase hydrolysis of fatty acids ex-vivo. Free fatty acid levels were measured by a commercially available enzymatic kit that detects all medium and long-chain acyl-CoAs with 90–100% recovery (NEFA-2hr, Wako Chemicals USA, Inc, Richmond, VA). Acylcarnitines were measured in plasma by electrospray tandem mass spectrometry as previously described [8]. Lactate, pyruvate, β-hydroxybutyrate and acetoacetic acid were measured in serum by gas chromatography-mass spectrometry [9].

Statistical Analysis

Blood analytes, and measures of exercise performance were collected for both exercise studies. Total area under the curve (TAUC) was calculated using the trapezoidal method for all parameters. The difference between the TAUC from the MCT and CHO supplemented tests were analyzed by paired t-tests with $p < 0.05$ being considered significant. The treatment effect and change over time during exercise testing was analyzed with a repeated

measures (RM) ANOVA. Post-hoc paired t-tests were used to determine time point differences if the treatment effect was significant. Participants in whom accurate HR and/or RER data was not collected during a given time interval were excluded from the average and statistical analysis of that time point. Statistical analysis of blood analytes excluded participants in whom blood samples were not collected due to IV failure. All analysis was conducted using Prism Software (Version 5.0, Graphpad, La Jolla, CA).

RESULTS

Demographics

All subjects completed both arms of the trial and contributed to the results reported (see Table 1). Eight patients, (average age = 12 yrs), had a diagnosis (dx) of LCHADD. All LCHADD participants had alpha-subunit mutations. Three participants (average age = 25 yrs) with adult-onset CPT2 (n=2) and VLCAD (n=1) deficiencies also participated in this study.

Substrate Oxidation Data

Respiratory Exchange Ratio—Total area under the curve (TAUC) for the MCT supplemented trial (3.648) was significantly lower than TAUC for the CHO supplemented trial (3.879; Figure 1). There was a significant MCT effect at baseline that increased over the course of the exercise trial [Fig 1 RM ANOVA: treatment (trt) $p = 0.012$, time $p = 0.004$]. The lower RER following MCT supplementation suggests that subjects oxidized more lipid during that bout of exercise than following CHO supplementation.

Oxygen Utilization—Because work performed was kept constant between trials, $V0_2$ in mL/kg/min did not significantly differ following MCT (VO_2TAUC = 56.72) versus CHO (VO_2TAUC = 48.34; Figure 2) supplementation. The level of exertion during both trials was approximately 4–4.5 metabolic equivalent tasks (METS). While treatment did not have a significant effect on $V0_2$, continuous exercise over 40 minutes did cause a significant increase in $V0_2$ over time ($V0_2$ RM ANOVA: trt $p = 0.0805$, time $p < 0.0001$).

Ketones—TAUC for serum ketone bodies (β-OH butyric acid and acetoacetic acid) was significantly higher when subjects (n=8) received MCT supplementation (TAUC = 802.8) prior to exercise versus pre-supplementation with CHO alone (TAUC = 169.8). The significant treatment effect was observed even prior to exercise (20 minutes after pre-exercise supplementation) but the increase with exercise over time was not significant (RM ANOVA: trt $p < 0.0001$; time $p= 0.0723$; see Figure 3a).

Acetylcarnitine—TAUC for acetylcarnitine (C2) following pre-exercise supplementation with MCT (TAUC = 21.08) was significantly greater than TAUC following pre-supplementation with CHO alone (TAUC = 13.66; n=8). The effect of MCT was observed at both pre and post exercise time points but did not change over time (RM ANOVA: trt $p = 0.001$, time $p = 0.412$). The significant increase in circulating acetylcarnitine following pre-supplementation with MCT (see Fig 3b) mimics the simultaneous change in ketones and illustrates the use of MCT to generate both acetyl-CoA and ketones for energy.

Free Fatty Acids—Plasma FFAs TAUC did not differ significantly in response to MCT (TAUC = 1.130) versus CHO (TAUC = 0.9841) pre-supplementation, as illustrated by Figure 3c (n=4). Duration of exercise did, however, cause a significant rise in FFAs during both exercise trials (RM ANOVA: trt $p = 0.3728$, time $p = 0.0009$).

Lactate & Pyruvate—TAUC for serum lactate and pyruvate (see Figure 4a & 4b) was significantly lower when subjects (n=8) received MCT supplementation (lactate TAUC = 2491; pyruvate TAUC = 189.1) prior to exercise versus CHO alone (lactate TAUC = 3198; pyruvate TAUC = 263.3). The magnitude of the treatment effect decreased over time (lactate RM ANOVA: trt $p = 0.0054$, time $p = 0.0002$; pyruvate RM ANOVA: trt $p < 0.0001$, time $p < 0.0001$); plasma lactate and pyruvate dropped significantly during exercise, and plateaued or rose upon recovery.

Sum of Long-Chain Acylcarnitines—TAUC for the sum of long-chain acylcarnitines following pre-exercise supplementation with MCT (TAUC = 6.180) was not significantly different than TAUC following pre-supplementation with CHO alone (TAUC = 5.202). Neither treatment nor time significantly affected the sum of long-chain acylcarnitine species (RM ANOVA: trt $p = 0.560$, time $p = 0.287$). Despite significant changes in RER, the data suggests that in the presence of MCT, overall β-oxidation of LCFAs and the formation of long-chain acylcarnitines remains unchanged (Table 2).

Creatine Kinase—All subjects fell within the normal range for creatine kinase (40–500 U/L) with the exception of 1 subject who exceeded this range before and after exercise pre-supplemented with CHO (see Table 3). Furthermore, there was not a significant difference in serum CK levels between interventions (TAUC MCT = 358.7, CHO = 530.6; RM ANOVA trt $p = 0.3366$, time $p = 0.9785$).

Heart Function Data

Heart Rate—Heart rate was significantly lower during the exercise pretreated with MCT (TAUC = 449.7) when compared to CHO alone (TAUC = 507.9; RM ANOVA: trt $p < 0.0001$). A statistically significant difference was also observed between time-points (RM ANOVA: time $p < 0.0001$); the magnitude of the difference in HR increased with exercise (see Figure 5a).

Double Product—There was no difference in systolic BP between trials; therefore, as a result of the drop in HR, a significantly lower double product (DP) resulted when subjects were supplemented with MCT versus CHO alone (RM ANOVA trt $p = 0.0134$). Duration of exercise did not significantly affect DP (RM ANOVA time $p = 0.7730$). An average difference of 1265.67 in DP was observed during the first half of exercise; during the second half of exercise DP differed by 2311 (Figure 5b).

DISCUSSION

The current exercise study was designed to explore energy metabolism and cardiac performance during exercise in response to pre-exercise isocaloric supplementation with MCT versus CHO. The findings suggest that substrate utilization and cardiac workload were altered and may enhance the ability of individuals with defects in fatty acid oxidation to tolerate aerobic activity.

The significant decrease in RER following MCT supplementation indicates a change in substrate oxidation, with an increase in FAO and decrease in CHO oxidation. While the RER suggests a whole body increase in FAO, it does not differentiate between the oxidation of medium versus long-chain fatty acids. The measured difference in FAO was not related to a difference in FA availability because plasma FFA concentrations rose during both exercise tests; thus, the increase in FAO seems linked to the availability of the MCT as a substrate. While defects in long-chain β-oxidation diminish the use of long-chain fatty acids for energy, lipolysis and mobilization of fatty acids appear to occur normally in this population.

Following MCT supplementation, the significant increase in ketone production, in subjects who usually produce minimal ketones, suggests that the liver is able to oxidize MCT and produce ketones in the presence of MCT. The increase in acetylcarnitine with MCT supplementation suggests that acetyl-CoA is also generated as an energy source. The decrease in glycolytic intermediates suggests that MCT decreases the oxidation of CHO and may lower the risk of exercise-induced lactic acidosis in these patients.

With medium-chain fatty acids as an alternate lipid substrate, total oxidation of fat increased. However, unlike a previous study [4], the rate of partial LCFA β-oxidation and production of long-chain acylcarnitines were not altered. In a previous study, plasma OH-acylcarnitines were reduced, suggesting that total LCFA oxidation was suppressed following MCT supplementation [4]. A difference between our current study and the previous research was that the participants' metabolic control was better in the current study compared to those in the previous study. It is possible that because our subjects were already in excellent metabolic control, sums of hydroxyacylcarnitines could not be further improved upon. Both studies, however, demonstrate the ability of MCTs to change substrate oxidation during exercise by bypassing the defect in LCFA oxidation and increasing the oxidation of medium-chain fatty acids.

Work performed was kept constant between the two exercise tests by repeating the same treadmill grade and speed. However, a significant decrease in cardiac workload, identified by an approximate 20 bpm drop in HR, was observed following MCT pre-supplementation. This finding may be associated with the concurrent shift in cardiac substrate oxidation. The heart requires a constant supply of energy; in the presence of both carbohydrate and lipid, the heart will utilize fatty acid in preference to glucose [10,11]. Furthermore, ketone bodies are oxidized in preference to fatty acids by cardiac muscle [12–14]. In contrast to the oxidation of long-chain fatty acids and glucose, the oxidation of ketones is simple, requiring only a few steps and is not subject to any regulatory processes. In comparison with other tissues in the body, the enzymes required for the conversion of 3-hydroxybutyrate to acetyl CoA are highly active in the heart and facilitate the use of ketone bodies as an alternative energy source[15,16].

Possible explanations of the change in cardiac workload observed in response to MCT pre-supplementation can be illustrated recognizing that cardiac output is a function of stroke volume and heart rate. Within subjects, cardiac output relates directly to oxygen uptake. As oxygen uptake was comparable between the two conditions, and because heart rate was lower, the stroke volume must have been greater with MCT supplementation.

Two hypotheses may explain that observation. First, MCT may have facilitated optimal contractile function and improved ejection fraction by increasing the preferred substrate of the myocardium, circulating ketone bodies.

Secondly, perhaps MCT itself temporarily provides a preferred substrate to generate ATP in the exercising cardiac and skeletal muscle. It is possible that in the absence of MCT and circulating ketone bodies, the heart compensates for the compromised ability to generate ATP by pumping harder, delivering more oxygen to the tissues in an effort to further ATP production and meet increased energy demands during a period of physical activity.

A similar change in HR has not been reported in healthy athletes given MCT prior to exercise [17,18]. We suspect this finding is unique to subjects with a long-chain FAO disorder. We propose that MCT may expand the usable energy supply, such as ketone bodies, and improve the oxidative capacity of the heart, primarily during a period of increased workload.

In conclusion, MCT supplementation prior to exercise altered substrate oxidation and decreased heart rate during that bout of exercise. We believe this effect is unique to subjects with an inherited defect in long-chain FAO and would not be observed in otherwise healthy individuals[18]. Experimentally, it was necessary to separate MCT and CHO to understand the etiology of the differences we observed; however, in practice, MCT will be better tolerated when mixed with a carbohydrate-containing beverage, which can also be used for fuel. MCT supplementation of approximately 0.3–0.4 gm/kg total body weight mixed with a CHO containing beverage may allow subjects with a long-chain FAO disorder to safely exercise at a moderate intensity (60–70% max heart rate) for up to an hour. The definition of "moderate" is largely dependent on individual fitness; however, bicycling (<10 mph), briskly walking (3–3.4 mph) and light to moderate calisthenics have all been regarded as moderate intensity activities based on the standard MET [19]. By altering substrate oxidation and decreasing heart rate in subjects with long-chain FAO disorders an active and healthy lifestyle can be facilitated.

Highlights

Patients with inherited disorders of long-chain fatty acid oxidation can experience repeated episodes of rhabdomyolysis with exercise. Providing a pre-exercise supplement to fuel exercise induced energy demands such as carbohydrates or medium chain triglycerides (MCT) may improve exercise tolerance. Pre-exercise supplementation with MCT significantly increased fat oxidation and lowered exercise heart rate during a moderate intensity treadmill exercise compared to carbohydrate supplementation. MCT supplementation prior to exercise lowers cardiac workload in patients with long-chain fatty acid oxidation disorders.

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Abbreviations

AUC	area under the curve
A-VO_2	arteriovenous oxygen
BMI	body mass index
BP	blood pressure
CHO	carbohydrate
CK	creatine kinase
CPT II	carnitine palmitoyl-transferase II
CTRC	Clinical & Translational Research Center
DEXA	dual energy x-ray absorpitometry

DP	double product
Dx	diagnosis
ECG	electrocardiography
EDTA	ethylenediaminetetraacetic acid
EF	ejection fraction
FAO	fatty acid oxidation
FFA	free fatty acid
FFM	fat free mass
GC/MS	gas chromatography/mass spectrometry
HR	heart rate
IC	indirect calorimetry
IRB	institutional review board
IV	intravenous
LBM	lean body mass
LCFA	long-chain fatty acid
LCHAD	long-chain 3-hydroxy acyl-CoA dehydrogenase deficiency
MCT	medium chain triglyceride
METS	metabolic equivalent tasks
RER	respiratory exchange ratio
RM	repeated measures
RQ	respiratory quotient
TAUC	total area under the curve
TFP	trifunctional protein
VCO_2	rate of elimination of carbon dioxide
VLCAD	very long-chain acyl-coenzyme A dehydrogenase
VO_2	oxygen uptake

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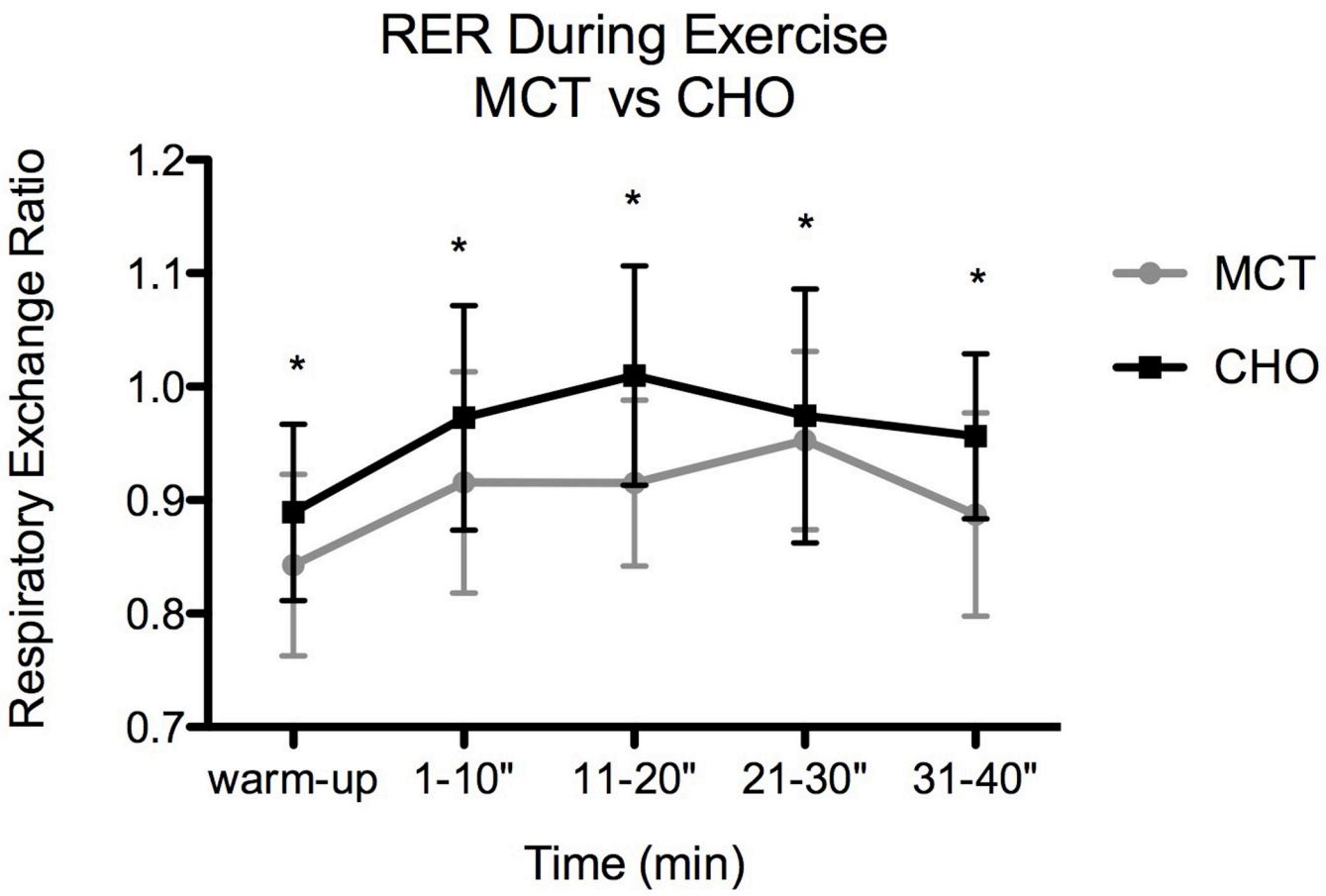

Fig 1.
Change in respiratory exchange ratio (RER) with and without MCT (*indicates significant difference). Standard deviation (SD) represented by error bars.

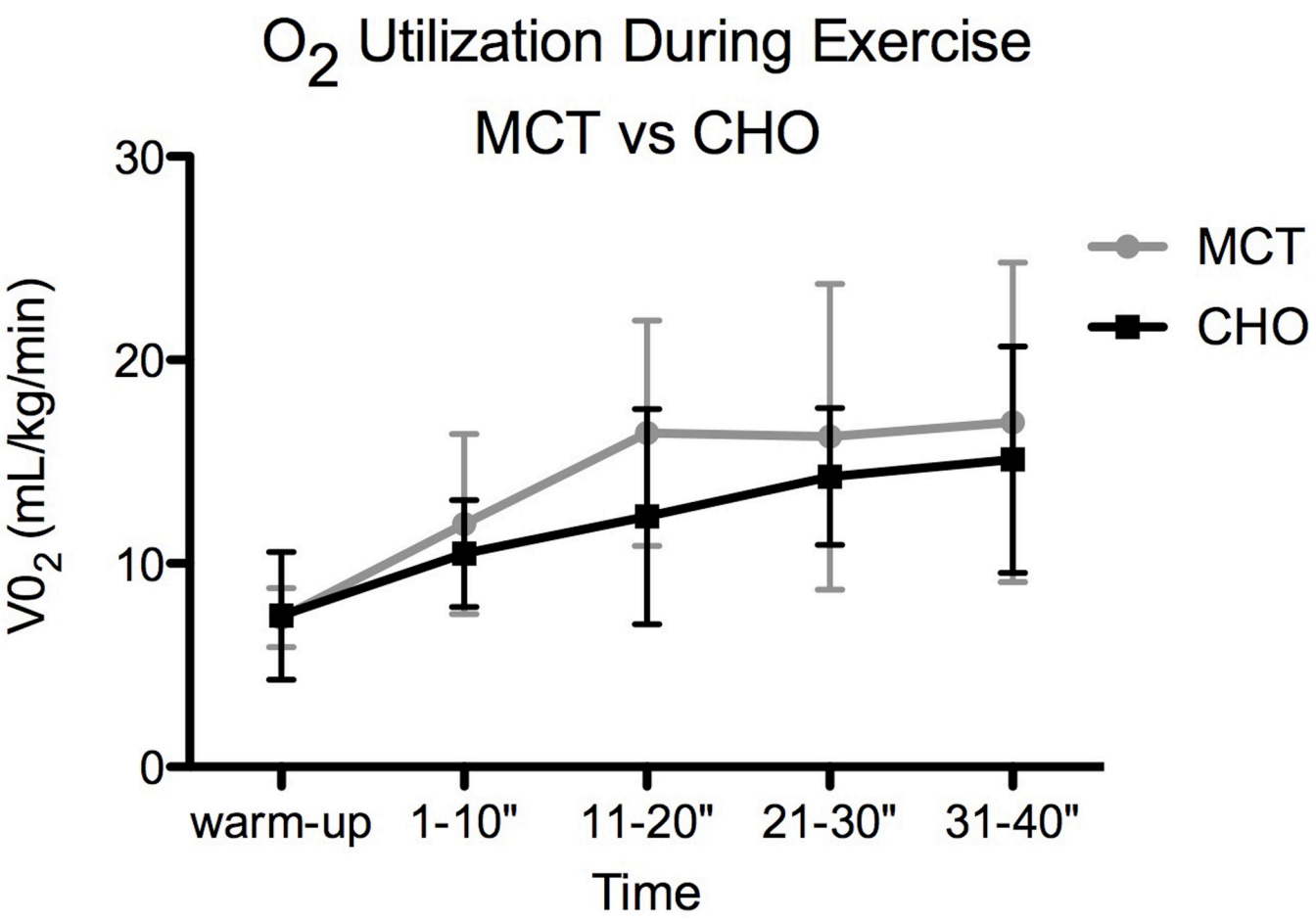

Fig 2.
Change in oxygen utilization during exercise.

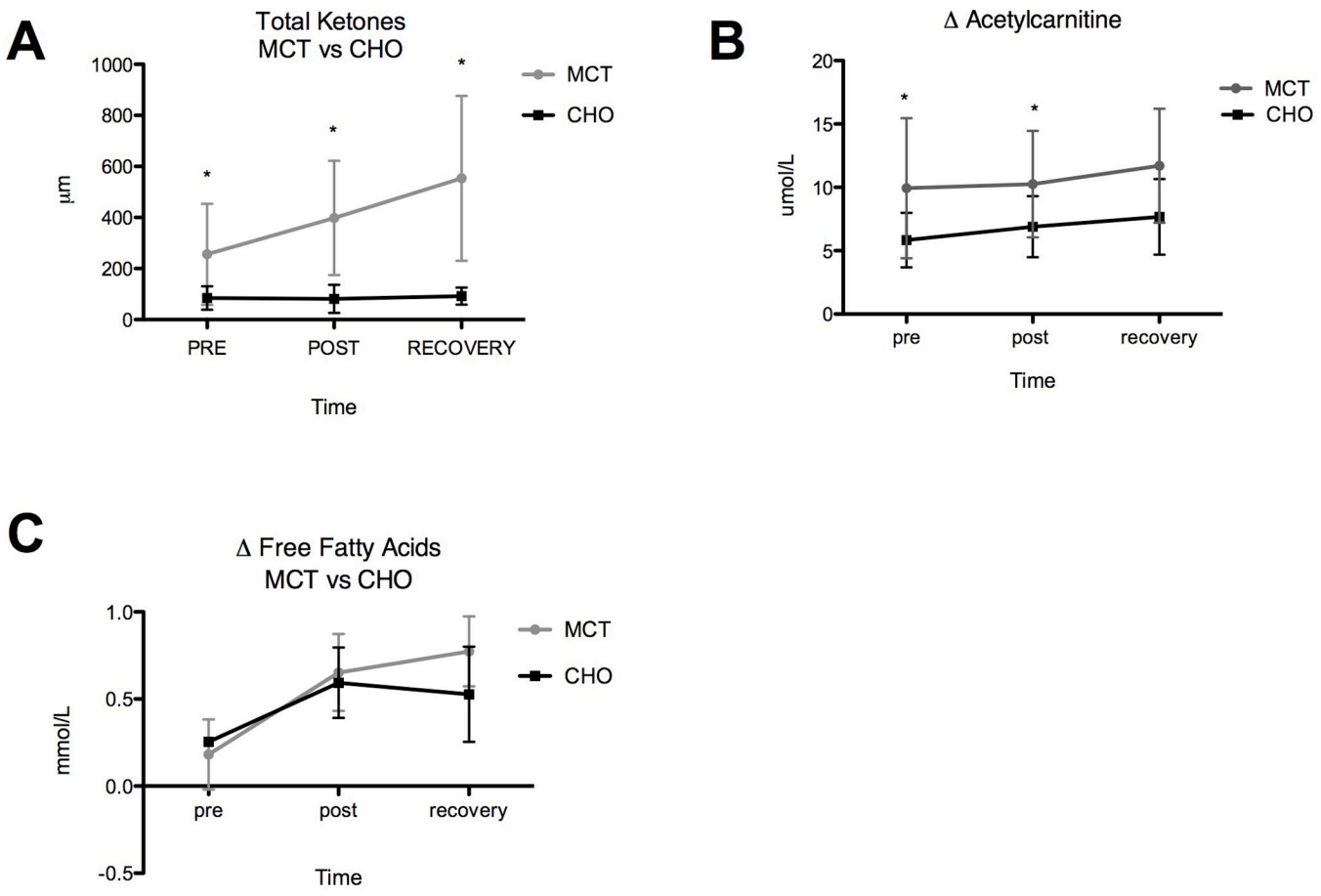

Fig 3.

(A) Change in total serum ketone bodies (B) acetylcarnitines and (C) free fatty acids, with and without MCT, measured immediately before, immediately after, and 20 minutes post exercise (*indicates significant difference).

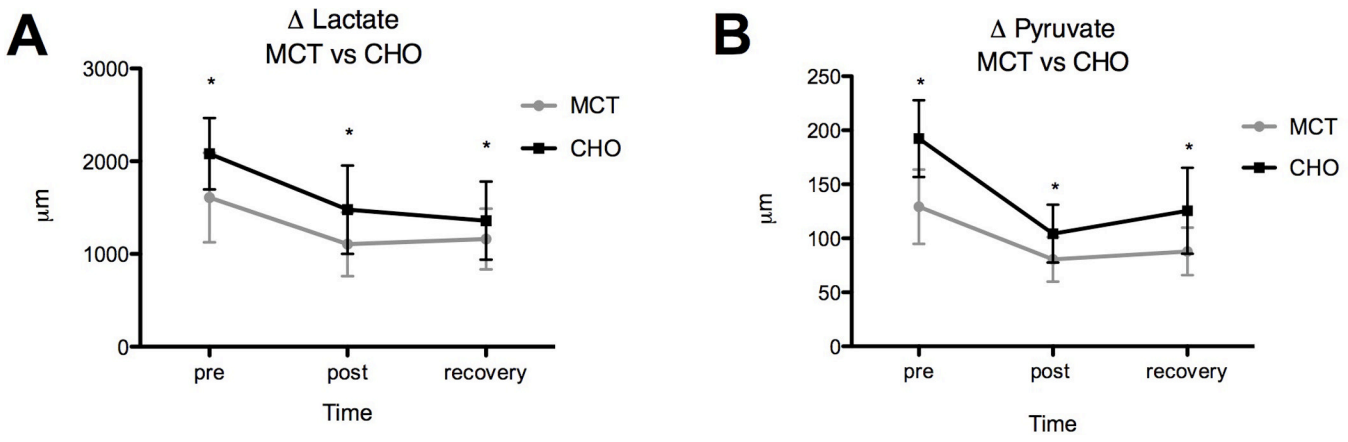

Fig 4.

Difference in glycolytic intermediates during exercise with and without MCT; (A) change serum lactate, (B) change in serum pyruvate, measured immediately before, immediately after, and 20 minutes post exercise (*indicates significant difference).

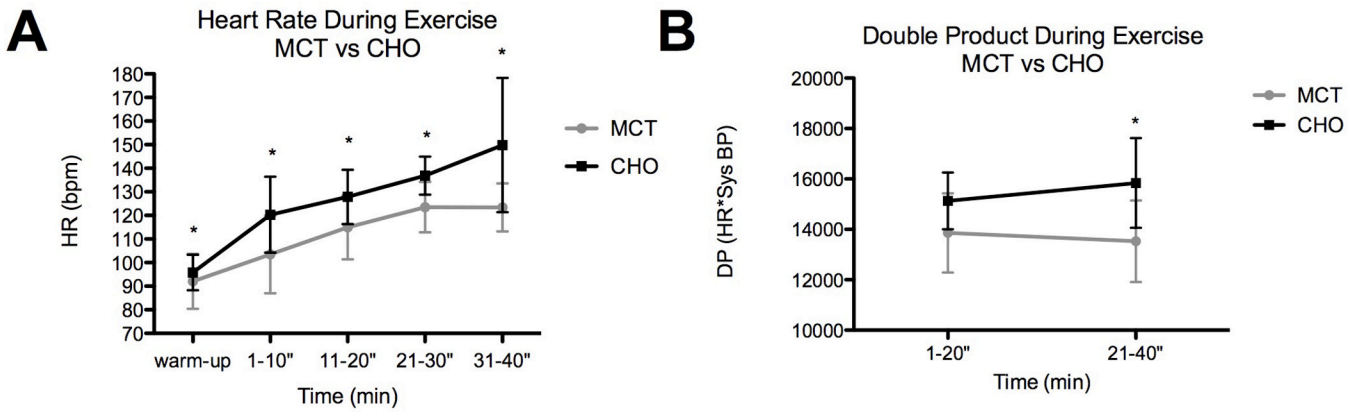

Fig 5.

Difference in heart function during exercise with and without MCT; (A) change in heart rate, (B) change in double product.

Table 1

Participant Characteristics

Subject	Dx	Gene	Mutation	Residual Enzyme Activity in Cultured Fibroblasts	Age (yrs)	Gender	BMI
1	VLCAD	ACADVL #609575	Not identified	0% of control VLCAD activity*	20	F	31.3
2	LCHAD	HADHA #600890	c. 1528G>C/ c.1528G>C		17	F	27.8
3	LCHAD	HADHA #600890	c. 1528G>C/ c.1528G>C	11.8** mol/min/mg protein	14	M	19.3
4	LCHAD	HADHA #600890	c.1528G>C/ c.1678C>T		16	M	23.8
5	LCHAD	HADHA #600890	c. 1528G>C/ c.1528G>C		7	M	16.6
6	CPT2	CPT2 #600650	Not available	20% of control CPT2 activity*	37	F	29.9
7	LCHAD	HADHA #600890	c. 1528G>C/ c.2102A>G		7	M	19.2
8	LCHAD	HADHA #600890	c. 1528G>C/ c.1528C>T		16	F	22.6
9	LCHAD	HADHA #600890	c.1528G>C/exon 3 splice A+3G		9	M	27.4
10	CPT2	CPT2 #600650	common mutations not detected***	0.060**** nmol/min/mg protein*	17	F	22.7
11	LCHAD	HADHA #600890	c.1528G> C/ c.1132C>T		8	M	18.8

Dx = diagnosis; VLCAD = very long-chain acylCoA dehydrogenase deficiency; LCHAD = long-chain 3-hydroxyacylCoA dehydrogenase deficiency; CPT2= Carnitine Palmitoyltransferase 2 deficiency; Gene = specific gene with disease associated mutations & OMIM #; yrs = years; F = Female; M = male; BMI = body mass index (weight in kilograms/ (height in meters)^2)

* diagnosis confirmed by disease specific change in acylcarnitines during bouts of rhabdomyolysis

** reference range for normal LCHAD activity = 43.6–89.9 nmol/min/mg protein

*** common mutations = p. 113S>L, p. 50P>H and p. 413 Q >fs; fs= frame shift

**** reference range for normal CPT 2 activity: 0.07 – 0.21 nmol/min/mg protein

Table 2

Mean changes in long chain acylcarnitines during exercise

	Sum long-chain acylcarnitines*(nmol/L)				
	MCT (n=8)		CHO (n=8)		MCT vs CHO
	Mean	+/−SD	Mean	+/−SD	paired t test (p)
Pre	2.036	1.198	2.119	1.172	0.857
Post	3.592	3.303	2.685	1.510	0.349
Recovery	3.139	2.403	2.915	1.902	0.711

*C12 + C12-0H + C12:1 + C12:1-0H + C14 + C14-0H + C14:1 + C14:1-0H + C14:2 + C16C + C16-0H + C16:1+ C16:1-0H+C18 + C18-0H+C18:1 + C18:1-0H + C18:2 + C18:2-0H

Table 3

Change in creatine kinase levels during exercise with and without MCT

	MCT (n=8)		CHO (n=8)		Paired t-test
	Mean	**+/− SD**	**Mean**	**+/− SD**	**p**
Pre	165	235	254	357	0.254
Post	182	243	265	370	0.287
Recovery	188	249	276	393	0.258