Medium-chain triglycerides (8:0 and 10:0) are promising nutrients for sarcopenia: a randomized controlled trial

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ABSTRACT

Background: The combined supplementation of medium-chain triglycerides (MCTs), L-leucine–rich amino acids, and cholecalciferol was previously shown to increase muscle strength and function in frail elderly individuals.

Objective: We examined whether treatment with MCTs alone is sufficient to increase muscle strength and function and activities of daily living (ADL) in such individuals.

Methods: We enrolled 64 elderly nursing home residents (85.5 ± 6.8 y) in a 3-mo randomized, controlled, single-blinded intervention trial. The participants were randomly assigned to 3 groups: the first group received supplemental L-leucine (1.2 g) and cholecalciferol (20 μg) enriched with 6 g/d of MCTs (LD + MCT group) as a positive control, the second group received 6 g/d of MCTs (MCT group) as a target, and the third group received 6 g/d of long-chain triglycerides (LCT group) as a negative control. Changes in muscle mass, strength, function, and ADL were monitored 4 times: at baseline, at 1.5 and 3 mo after initiation of the intervention (intervention), and 1.5 mo after termination of the intervention (washout).

Results: The 64 participants randomly assigned to the 3 groups were included in an intention-to-treat analysis. Forty-eight participants completed the study and were included in a per-protocol analysis. At 3 mo, participants in the MCT group had a 48.1% increase in 10-s leg open and close test performance [intention-to-treat adjusted means: MCT 2.28 n/10 s (1.37, 3.19) compared with LCT −0.59 n/10 s (−1.52, 0.35), $P < 0.05$], a 27.8% increase in a 30-s repetitive saliva swallowing test [MCT 0.5 n/30 s (0.1, 1.0) compared with LCT −0.5 n/30 s (−0.9, 0.0), $P < 0.05$], and a 7.5% increase in Functional Independence Measure score, a questionnaire for assessing ADL [MCT 5.6 points (1.3, 9.9) compared with LCT −6.6 points (−11.3, −2.0), $P < 0.05$].

Conclusion: MCTs (6 g/d) could increase the muscle strength and function of frail elderly individuals and also improve their ADL. This trial was registered at the University Hospital Medical Information Network Clinical Trial Registry as UMIN000023302. *Am J Clin Nutr* 2019;00:1–14.

Keywords: MCT, leucine, sarcopenia, frailty, elderly, muscle atrophy

Introduction

Sarcopenia is a syndrome characterized by the loss of skeletal muscle mass, strength, and function that occurs as a consequence of aging (1). Muscle mass represents a main determinant of muscle strength and has been strongly associated with performance in the activities of daily living (ADL) and level of independence in elderly individuals (2). An adequate diet is needed to maintain muscle mass, but it is difficult to increase the dietary intake of some elderly participants due to decreased appetite and digestive activity (3, 4). Thus, a useful intervention for elderly individuals would be to supplement their diet with small amounts of nutrients that they could easily ingest and would preserve their muscle mass and function.

A 3-mo randomized, controlled, single-blinded, parallel group trial was previously conducted to find a combination of nutrients that could be used to treat sarcopenia (5, 6). The participants were randomly assigned to 3 groups: the first group received a daily administered supplement of L-leucine (1.2 g) and

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Supplemental Tables 1–3 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: AC, mid-upper-arm circumference; ADL, activities of daily living; AMA, mid-upper-arm muscle area; CC, calf circumference; FFM, fat-free mass; FIM, Functional Independence Measure; HTLV-1, human T-cell leukemia virus-1; LCT, long-chain triglyceride; LCT group, participants receiving LCTs only; LD, leucine- and cholecalciferol-enriched supplement; LD + MCT, a leucine- and cholecalciferol-enriched supplement with 6 g of MCTs; LD + MCT group, participants receiving a leucine- and cholecalciferol-enriched supplement with MCTs; MCT, medium-chain triglyceride; MCT group, participants receiving MCTs only; PEF, peak expiratory flow; RSST, repetitive saliva swallowing test; TSF, triceps skinfold thickness.

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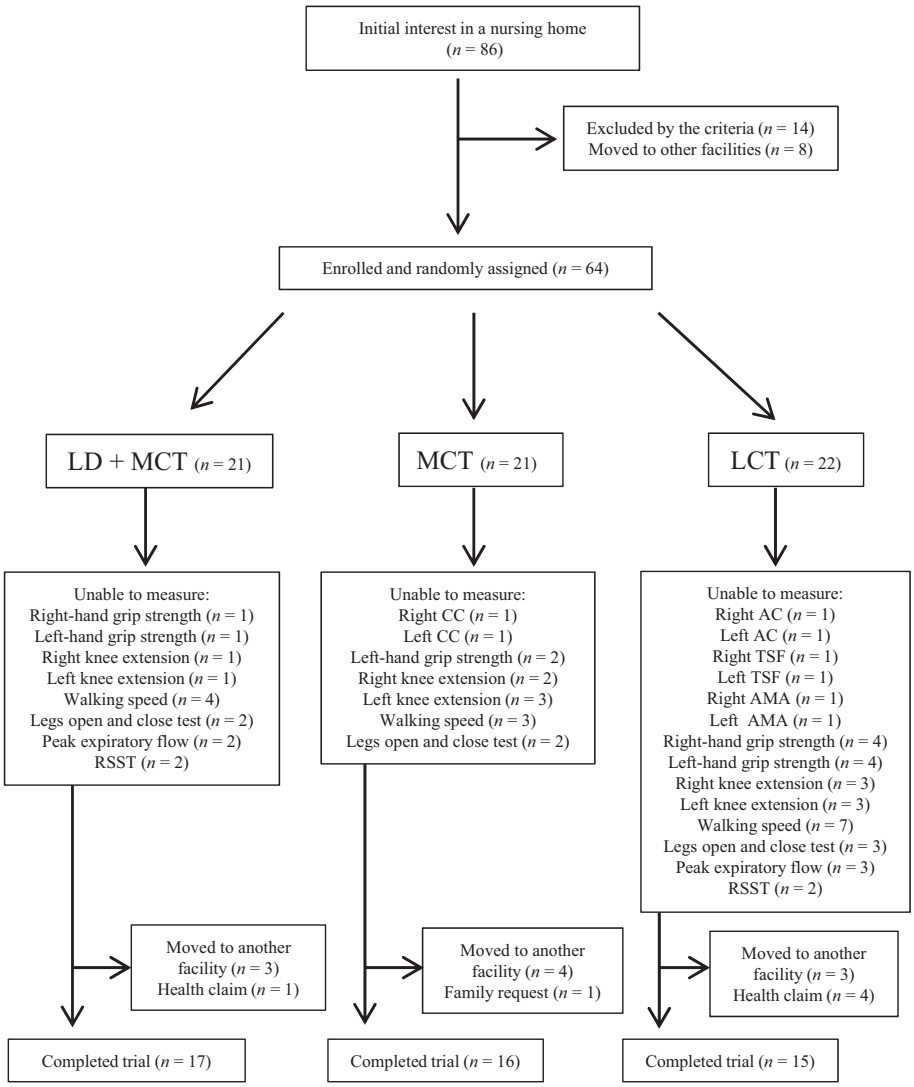

FIGURE 1 Trial profile. Intention-to treat analysis included all participants who were randomly assigned to 3 groups: the LD + MCT group, MCT group, and LCT group ($n = 64$). Per-protocol analysis included all participants who completed the study ($n = 48$). AC, mid-upper-arm circumference; AMA, mid-upper-arm muscle area; CC, calf circumference; LCT, 6 g of long-chain triglycerides; LD + MCT, leucine- and cholecalciferol-enriched supplement with 6 g of medium-chain triglycerides; MCT, 6 g of medium-chain triglycerides; RSST, repetitive saliva swallowing test; TSF, triceps skinfold thickness.

cholecalciferol (20 μg) with 6 g of medium-chain triglycerides (LD + MCT), the second group received the same supplement with 6 g of long-chain triglycerides (LD + LCT), and the third group did not receive any supplements (nonsupplement). The administration of L-leucine– (7–9) and cholecalciferol-enriched (10, 11) supplements might improve the muscle function of elderly individuals. After 3 mo, the participants in the LD + MCT group had increased right-hand grip strength, walking speed, 10-s leg open and close test performance, and peak expiratory flow (PEF). No significant improvements were observed in muscle mass, strength, and function of the LD + LCT or nonsupplement groups. It was concluded that MCTs (6 g/d) played a pivotal role in the increased muscle strength and function in frail elderly individuals. However, because we could not create an MCTs-only group, due to the limited number of participants, it was not clear whether the favorable effects observed in the LD + MCT group were due to MCTs or the interaction between MCTs and LD. To answer this question, we performed an intervention study that included 3 groups: LD + MCT (positive control), MCTs only (target), and LCTs only (negative control), with a time course that included a washout period.

Methods

Participants

The trial was announced in early August 2016 at the Day Care SKY facility in Yokohama, Japan. All participants who resided in this nursing home and who required special care from a helper were targeted ($n = 86$) (**Figure 1**). The registration started on 25 August, 2016 and ended on 9 September, 2016. During this interval, 14 participants were excluded by the following criteria: a BMI of >23 kg/m^2 (to avoid a further increase in body weight); aged <65 y; parenteral nutrition; difficulty in swallowing; severe

heart failure; lung, liver, kidney, or blood disease; a fasting blood glucose concentration of ≥200 mg/dL; a blood creatinine concentration of ≥1.5 mg/dL; a C-reactive protein concentration of ≥2.0 mg/dL; or allergy to the supplements used in the study, and 8 participants were moved to other facilities, as described in Figure 1. Thus, 64 participants (13 men, 51 women; mean age 85.5 ± 6.8 [±SD] y) were enrolled and assigned to each group on 10 September, 2016. Data collection at baseline was started on 11 September, 2016 and ended by 21 September, 2016. The intervention took place from 22 September, 2016 to 20 December, 2016 at Day Care SKY.

The participants and their family members were informed of the nature of the experimental procedures before their written informed consent was obtained. In patients with cognitive decline or difficulty in writing (n = 30), informed consent was obtained from the patient's family members. The present study was approved by the Human Ethics Committee of Showa Women's University (Nos. 16–17 and 16–49). The procedures were conducted in accordance with either the ethical standards of the Institutional Committee on Human Experimentation or the Helsinki Declaration of 1975 (as revised in 1983).

Study design

We performed a 3-mo randomized, controlled, single-blinded, parallel group intervention trial in which the 64 participants were randomly assigned into 3 groups (Figure 1). Sealed envelopes containing the written informed consent of the individual participants (or their family members) were thoroughly shuffled. Twenty-one participants (envelopes) each were assigned to the first and second groups, and 22 participants were assigned to the third group. Allocation was conducted by a person who was not a member of this study.

The first group (n = 21; 4 men, 17 women; mean age 85.6 ± 6.3 y) received a leucine- and cholecalciferol-enriched supplement with MCTs as a positive control group (LD + MCT group), based on a previous study (5). To examine the effects of MCTs, the second group (n = 21; 5 men and 16 women; mean age 84.9 ± 6.9 y) received MCTs only (MCT group). The third group (n = 22; 4 men and 18 women; mean age 86.1 ± 7.2 y) received LCTs only as a negative control group (LCT group).

Participants' body weight, appendicular muscle mass, strength, function, and ADL were assessed at 4 equally spaced time points; at baseline, at 1.5 and 3 mo after the initiation of the intervention (intervention), and at 1.5 mo after the termination of the intervention (washout).

The food records of the individual participants were collected every day for 3 mo during the baseline period, 3 mo during the intervention period, and for an additional 1.5 mo during the washout period. Doctors, nurses, and helpers monitored the gastrointestinal and other symptoms, including the defecation state of the participants, every day during the 3-mo intervention period.

Blinding

The tube containing the supplement (LD) was visible to the participants; thus, the participants in the LD + MCT group could not be blinded. However, the participants could not distinguish between the MCTs and LCTs supplements.

To assess the outcomes, the examiners who oversaw the walking speed test and undertook the Functional Independence Measure (FIM) were unaware of each participant's group. Other assessments [anthropometric measurements, hand grip strength, knee leg extension time, leg open and close test, PEF test, and repetitive saliva swallowing test (RSST)] were conducted by an expert with a certificate of training but who was aware of the participant's group assignment.

Study products

The leucine- and cholecalciferol-enriched supplement (Amino Care Jelly Leucine 40 containing Amino L40) was packaged in tubes purchased from Ajinomoto Inc. The jelly containing essential amino acids (3 g) [leucine (1.2 g), isoleucine (0.3 g), valine (0.3 g), other amino acids (1.2 g)], carbohydrate (9.7 g), sodium (75 mg), cholecalciferol (20 μg, 800 IU), thiamin (0.2 mg), pyridoxine (0.2 mg), cyanocobalamin (0.4 μg), and water (87 g) was ingested by sucking it from a tube, as described previously (5). The leucine- and cholecalciferol-enriched supplement contained 30 kcal yet comprised 9.7 g carbohydrate and 3.0 g of amino acids because carbohydrate may contain energy-less carbohydrates (e.g., dietary fiber and resistant starch).

The MCTs (75% 8:0 and 25% 10:0 from total fatty acids) and LCTs (64% 18:1, 19% 18:2, and 9% 18:3 from total fatty acids) were purchased from Nisshin OilliO Group Ltd. The fatty acid compositions have been previously described in detail (5). Six grams of MCTs (50 kcal; 8.3 kcal/g) or LCTs (54 kcal; 9 kcal/g) per day were mixed with foods such as steamed rice or miso soup at dinnertime. In total, the participants in the LD + MCT group were estimated to increase their energy intake by ∼30 kcal/d in comparison to the other groups.

Dietary intake

Breakfast, lunch, and dinner were served daily in the nursing care home. The habitual daily energy and nutrient intake of the individual participants during the baseline, intervention, and washout periods were measured as described previously (5). The mean daily energy and nutrient intakes of the groups were then calculated based on the daily energy and nutrient intakes of the individual participants (**Table 1**).

Daily activity and rehabilitation/exercise

The daily activities of this nursing care home were as follows: at 0715 h, exercises for the mouth, including speaking and moving the tongue and the corners of the mouth, were started for 10 min, for which all residents were required to attend. At 1000 h, exercises for the arms and fingers were started for 20 min, for which attendance was voluntary. At 1530 h, recreational therapy, including drawing pictures, calligraphy, viewing a movie, playing cards, origami, or karaoke, was started for 1 h, for which attendance was voluntary. At other times, residents spent their free time watching TV, lying in bed, and doing other activities.

TABLE 1 Dietary intake at baseline and during the 3-mo intervention and the changes in the LD + MCT, MCT, and LCT groups (per-protocol analysis set, $n = 48$)[1]

Measure and group	n	Baseline	Intervention	Change (95% CI)	% Change[2]
Energy					
kcal/d					
LD + MCT	17	1376 ± 208	1433 ± 214	57 (6, 108)	4.1
MCT	16	1364 ± 268	1411 ± 257	47 (−6, 100)	3.4
LCT	15	1371 ± 327	1448 ± 321	77 (22, 131)	5.6
P value[3]				0.73	
kJ/d					
LD + MCT	17	5761 ± 870	5998 ± 895	239 (24, 453)	4.1
MCT	16	5709 ± 1121	5909 ± 1075	197 (−24, 418)	3.5
LCT	15	5742 ± 1369	6063 ± 1342	322 (93, 550)	5.6
P value				0.73	
Protein					
en%					
LD + MCT	17	15.8 ± 1.6	16.3 ± 1.1	0.3 (−0.4, 0.9)	1.9
MCT	16	16.2 ± 2.4	16.1 ± 2.5	− 0.1 (−0.8, 0.5)	− 0.6
LCT	15	16.6 ± 2.3	15.5 ± 1.6	− 0.9 (−1.6, −0.2)	− 5.4
P value				0.06	
g/d					
LD + MCT	17	54.4 ± 9.2	57.9 ± 6.8	3.5 (1.4, 5.5)	6.4
MCT	16	54.2 ± 7.6	55.7 ± 7.0	1.5 (−0.6, 3.5)	2.8
LCT	15	55.4 ± 9.6	55.8 ± 11.3	0.5 (−1.6, 2.7)	0.9
P value				0.13	
g/(kg BW · d)					
LD + MCT	17	1.3 ± 0.3	1.4 ± 0.3	0.1 (0.0, 0.1)[a]	7.7
MCT	16	1.3 ± 0.3	1.3 ± 0.2	− 0.0 (−0.1, 0.0)[b]	− 0.0
LCT	15	1.2 ± 0.3	1.2 ± 0.3	− 0.0 (−0.1, 0.0)[a, b]	− 0.0
P value				0.021	
Leucine, g/d					
LD + MCT	17	4.6 ± 0.7	5.8 ± 6.0	1.3 (1.1, 1.4)[a]	28.3
MCT	16	4.2 ± 0.6	4.3 ± 0.6	0.1 (−0.1. 0.2)[b]	2.4
LCT	15	4.6 ± 0.5	4.6 ± 0.4	0.0 (−0.1. 0.2)[b]	0.0
P value				<0.001	
EAAs, g/d					
LD + MCT	17	22.8 ± 2.9	25.7 ± 2.5	2.9 (2.2, 3.7)[a]	12.7
MCT	16	21.3 ± 3.1	21.9 ± 2.8	0.5 (−0.3, 1.2)[b]	2.3
LCT	15	22.7 ± 2.9	22.5 ± 3.7	− 0.2 (−0.9, 0.6)[b]	− 0.9
P value				<0.001	
Carbohydrate,					
en%					
LD + MCT	17	63.0 ± 2.8	59.7 ± 3.8	− 3.4 (−4.8, −2.0)	− 5.4
MCT	16	61.8 ± 6.9	57.7 ± 8.6	− 4.1 (−5.5, −2.7)	− 6.6
LCT	15	61.3 ± 5.9	59.6 ± 5.6	− 1.6 (−3.1, −0.1)	− 2.6
P value				0.06	
g/d					
LD + MCT	17	217 ± 36	215 ± 40	− 2 (−13, 8)	− 0.9
MCT	16	214 ± 57	208 ± 61	− 6 (−17, 5)	− 2.8
LCT	15	213 ± 61	218 ± 60	5 (−6, 17)	2.3
P value				0.33	
Fat					
en%					
LD + MCT	17	21.2 ± 2.7	24.1 ± 3.0	2.9 (1.9, 4.0)	13.7
MCT	16	21.9 ± 4.6	26.2 ± 6.1	4.2 (3.2, 5.3)	19.2
LCT	15	22.2 ± 3.8	24.8 ± 4.3	2.6 (1.5, 3.7)	11.7
P value				0.08	
g/d					
LD + MCT	17	32.3 ± 5.7	38.1 ± 6.1	5.8 (4.6, 7.1)	18.0
MCT	16	32.3 ± 5.0	39.7 ± 5.3	7.4 (6.1, 8.7)	22.9
LCT	15	33.1 ± 7.5	39.1 ± 7.7	6.0 (4.6, 7.3)	18.1
P value				0.16	
MCT (8:0 + 10:0), mg/d					
LD + MCT	17	161 ± 140	6162 ± 146	6000 (5978, 6022)[a]	3727
MCT	16	186 ± 242	6206 ± 244	6020 (5998, 6042)[a]	3237
LCT	15	196 ± 181	208 ± 175	12 (−11, 35)[b]	6
P value				<0.001	

(*Continued*)

TABLE 1 (*Continued*)

Measure and group	*n*	Baseline	Intervention	Change (95% CI)	% Change[2]
Sodium, mg/d					
LD + MCT	17	2883 ± 782	2893 ± 858	10 (−133, 153)	0.3
MCT	16	2881 ± 767	2979 ± 828	99 (−49, 246)	3.4
LCT	15	2686 ± 1046	2797 ± 1034	110 (−43, 263)	4.1
P value				0.57	
Thiamin, mg/d					
LD + MCT	17	0.8 ± 0.2	1.0 ± 0.2	0.2 (0.1, 0.2)[a]	25.0
MCT	16	0.9 ± 0.3	0.9 ± 0.3	0.0 (0.0, 0.0)[b]	0.0
LCT	15	0.8 ± 0.3	0.8 ± 0.3	0.0 (−0.0, 0.1)[b]	0.0
P value				<0.001	
Pyridoxine, mg/d					
LD + MCT	17	1.0 ± 0.2	1.3 ± 0.3	0.3 (0.2, 0.4)[a]	30.0
MCT	16	1.1 ± 0.4	1.1 ± 0.4	0.0 (−0.1, 0.1)[b]	0.0
LCT	15	1.0 ± 0.4	0.9 ± 0.4	− 0.1 (−0.2, 0.0)[b]	− 10.0
P value				<0.001	
Cyanocobalamin, μg/d					
LD + MCT	17	3.2 ± 0.6	3.5 ± 0.8	0.3 (0.0, 0.5)	9.4
MCT	16	3.2 ± 0.7	3.3 ± 1.0	0.2 (−0.1, 0.4)	6.3
LCT	15	3.1 ± 0.8	3.2 ± 0.8	0.2 (−0.1, 0.4)	6.5
P value				0.82	
Vitamin D,[4] μg/d					
LD + MCT	17	3.5 ± 1.0	23.4 ± 1.2	19.9 (19.6, 20.1)[a]	568.6
MCT	16	3.6 ± 0.8	3.7 ± 0.9	0.1 (−0.2, 0.3)[b]	2.8
LCT	15	3.3 ± 1.2	3.4 ± 1.4	0.1 (−0.1, 0.4)[b]	3.0
P value				<0.001	

[1]Values are expressed as the mean ± SD or adjusted mean (95% CI). The adjusted mean changes in columns without a common superscript letter showed statistically significant differences between the groups, $P < 0.05$. BW, body weight; EAA, essential amino acid; en%, percentage of energy; LCT, 6 g of long-chain triglycerides; LD + MCT, leucine- and cholecalciferol-enriched supplement with 6 g of medium-chain triglycerides; MCT, 6 g of medium-chain triglycerides.

[2]% Change = adjusted mean change from baseline/mean of baseline value × 100.

[3]*P* value represents the difference in the change in a variable among the groups, as assessed by a 1-factor ANCOVA adjusted for each baseline value.

[4]Vitamin D includes both cholecalciferol and ergocalciferol.

In addition, rehabilitation/exercise protocols were individually conducted. Initially, lifestyle goals, such as maintaining a life rhythm throughout the day, preventing falls, and living independently, were proposed for the individuals. To meet these goals, several types of exercises such as walking, resistance training, leg stretches, stair-stepping, or balance training were individually conducted for 20 min twice a week.

The individual daily activities and rehabilitation/exercise were not changed during the baseline, intervention, or washout periods. The conductors of the daily activity and individual rehabilitation/exercise were unaware of the group to which each participant was assigned.

Medications

Medical drugs (antihypertensive, antiplatelet, antipsychotic, antilipemic, antidiabetic, antiosteoporosis, laxative, and hypnotic drugs), which were used by some of the participants, were not changed during the baseline, intervention, or washout periods.

Anthropometric analysis

The methods used for the anthropometric analysis were the same as used in our previous study (5). The mid-upper-arm circumference (AC) and bilateral calf circumference (CC) were measured using a flexible, nonstretch tape (Inser-Tape, Medical Science Publications Inc.). The triceps skinfold thickness (TSF) was measured using a skinfold caliper (Adipometer, Medical Science Publications Inc.) according to the standard procedure. The mid-upper-arm muscle area (AMA) was calculated as follows: $\text{AMA} = [\text{AC (cm)} - \pi \times \text{TSF (cm)}]^2/(4 \times \pi)$ (12). One participant in the LD + MCT group was left-handed due to paralysis of the right hand, and all others were right-handed. Two participants in the LCT group had bone fracture of the right and left hand, respectively (Figure 1) and were excluded from analyses of the arm. One participant in the MCT group had bilateral leg edema and was excluded from the analysis of CC.

Muscle strength and endurance

Upper extremity strength was measured by hand-grip dynamometry, as described previously (5). Two participants in the LD + MCT group had paralysis of the right and left hand, respectively. Two participants in the MCT group had paralysis of the left hand. Two participants in the LCT group had paralysis of both hands, 2 participants had bone fracture of the right and left hand, respectively, and another participant did not understand the test methods. These 9 participants were excluded from the analysis.

Muscle endurance in the lower extremities was estimated based on the length of time that the participant could hold each lower leg in the horizontal position, with the participant seated in a straight-backed chair (knee extension time), as described previously (5). One participant in the LD + MCT group did not understand the test method. One participant in the MCT group had myelopathy related to human T-cell leukemia virus type 1 (HTLV-1), a second participant had left foot paralysis, and another participant had hip osteoarthritis. Two participants in the LCT group had bilateral leg paralysis, and another participant did not understand the test methods. These 7 participants were excluded from the analysis.

Walking speed

Walking speed was calculated from the time and distance completed by each participant, as described previously (5). Two participants in the LD + MCT group did not understand the test method, and 2 participants could not walk due to muscle weakness. One participant in the MCT group could not walk due to muscle weakness, a second participant had myelopathy related to HTLV-1, and another participant had hip osteoarthritis. Five participants in the LCT group could not walk due to muscle weakness, a second participant had left foot paralysis, and another participant refused rehabilitation. These 14 participants were excluded from the analysis.

Leg open and close test (seated)

With the participant sitting in a chair, the number of iterations of opening and closing of the legs during a 10-s period was counted, as described previously (5). Two participants in the LD + MCT group did not understand the test method. One participant in the MCT group had myelopathy related to HTLV-1, and another participant had hip osteoarthritis. Two participants in the LCT group had right and left foot paralysis, and another participant did not understand the test method. These 7 participants were excluded from the analysis.

Respiratory function

To estimate the strength of the respiratory muscles, PEF was measured using a peak flow meter (Scientific Molding Corporation Ltd.), as described previously (5). Participants whose recorded PEF values were zero (2 participants in the LD + MCT group and 3 participants in the LCT group) were excluded from the analysis because it was not clear whether these participants understood the method or whether their PEF value was below the limit of detection.

Swallowing function

The swallowing function was estimated based on the RSST. The participants were asked to swallow saliva as many times as possible over 30 s when in a seated position; during this time, the number of elevations of the hyoid bone and the laryngeal prominence was counted. This test was not conducted in the previous study (5). Two participants in the LD + MCT group and 2 participants in the LCT group did not understand the test method and were excluded from the analysis.

ADL

The participants' ADL were estimated based on the FIM (13, 14), in which the caregiver answered questions about the participant. There are 18 items (total 126 points) in the FIM, of which the first 13 items (total 91 points) represent measures of motor function and the last 5 items (total 35 points) represent measures of cognitive function (13, 14). A higher score indicates better ADL.

Primary and secondary outcome variables and sample size

The primary outcome of the trial was the 10-s leg open and close test, which showed the largest increase (2.31/10 s, 68.2%; $P < 0.001$) in the LD + MCT group, and is among the muscle tests conducted in the previous study (5). The secondary outcomes were right TSF, calculated right AMA, right-hand grip strength, right and left knee extension times, walking speed, PEF, RSST, and FIM score. For the primary efficacy measure for the 10-s leg open and close test, 29 participants were required in 1 group ($n = 87$ in 3 groups) for a power of 80% at a 2-sided α of 0.05 to detect a treatment difference of 2.31/10 s with an SD of 3.09/10 s.

Statistical analysis

All data are expressed as means ± SD or adjusted means (95% CI). Analyses of primary and secondary endpoints were conducted using a linear mixed model that followed the intention-to-treat principle (i.e., dropout participants were included in the analysis). In this model, the dependent metric-scaled variables were the changes from the baseline values at the 1.5-mo and 3-mo interventions and at washout. The independent categorical variables (fixed factors) were groups (LD + MCT, MCT, and LCT), time (1.5-mo and 3-mo interventions and washout), and the interaction between group and time.

The following covariates were taken into account in the analysis: in model 1, the baseline value of the respective change, and in model 2, additional adjustment for age, sex, BMI (a marker of nutritional state), right-hand grip strength (a marker of sarcopenia), and total FIM score (a marker of ADL including cognitive function) at baseline, all of which represent basal characteristics of the participants that might affect their response to MCTs. The statistical results of model 1 and model 2 are shown in **Supplemental Tables 1–3** and **Tables 2–4**, respectively.

If the main effect of the group was significant, but the group-by-time interaction was nonsignificant, the overall changes (mean of 3 time points) between the groups were compared, and their results are indicated by a superscript letter to the right of the words "LD + MCT," "MCT," and "LCT" in Tables 2–4 and Supplemental Tables 1–3. If both the main effect of the group and the group-by-time interaction were significant, posthoc tests with Bonferroni correction were performed to compare the changes between groups at each time point (between-group analysis) or the changes at the 3-mo intervention with other time points within groups (within-group analysis), whereas the overall changes (mean of 3 time points) between the groups was not

TABLE 2 Anthropometric measurements at baseline, and changes from baseline at 1.5 and 3 mo after the initiation of the intervention (intervention) and at 1.5 mo after the termination of the intervention (washout) in the LD + MCT, MCT, and LCT groups in model 2 (adjusted for each baseline value and other confounders) (intention-to-treat analysis set, $n = 64$)[1]

			Change (95% CI), % change[3]			Fixed effects[4]		
Measure and group	n[2]	Baseline	1.5-mo intervention	3-mo intervention	Washout	Group	Time	Group by time
Body weight, kg								
LD + MCT	21, 21, 18, 17	41.2 ± 6.4	0.5 (−0.3, 1.4), 1.2	0.3 (−0.5, 1.2), 0.7	0.4 (−0.5, 1.2), 1.0			
MCT	21, 21, 16, 16	42.8 ± 10.8	0.8 (0.0, 1.7), 1.9	1.3 (0.4, 2.1), 3.0	0.8 (−0.0, 1.7), 1.9			
LCT	22, 22, 15, 15	43.6 ± 6.7	0.0 (−0.8, 0.9), 0.0	0.1 (−0.8, 1.0), 0.2	− 0.0 (−0.9, 0.9), −0.0			
P value						0.25	0.63	0.69
BMI, kg/m^2								
LD + MCT	21, 21, 18, 17	18.4 ± 2.2	0.3 (−0.1, 0.7), 1.6	0.2 (−0.2, 0.6), 1.1	0.3 (−0.2, 0.7), 1.6			
MCT	21, 21, 16, 16	18.2 ± 3.3	0.4 (0.0, 0.8), 2.2	0.6 (0.2, 1.0), 3.3	0.4 (−0.1. 0.8), 2.2			
LCT	22, 22, 15, 15	19.0 ± 1.9	0.0 (−0.4, 0.4), 0.0	−0.0 (−0.5, 0.4), −0.0	− 0.1 (−0.5, 0.3), −0.5			
P value						0.24	0.53	0.65
Right AC, cm								
LD + MCT	21, 21, 18, 17	21.3 ± 3.1	0.1(−0.2, 0.5), 0.5	0.5 (0.1, 0.9), 2.3	0.2 (−0.2, 0.6), 0.9			
MCT	21, 21, 16, 16	21.9 ± 4.0	0.3 (−0.1, 0.6), 1.4	0.5 (0.2, 0.9), 2.3	0.3 (−0.0, 0.7), 1.4			
LCT	21, 21, 15, 15	22.5 ± 2.4	−0.0 (−0.4, 0.3), −0.0	0.2 (−0.2, 0.6), 0.9	− 0.0 (−0.4, 0.4), −0.0			
P value						0.41	0.001	0.99
Left AC, cm								
LD + MCT	21, 21, 18, 17	21.0 ± 2.4	0.1 (−0.2, 0.4), 0.5	0.4 (0.1, 0.8), 1.9	0.1 (−0.2, 0.4), 0.5			
MCT	21, 21, 16, 16	21.8 ± 3.9	0.1 (−0.2, 0.4), 0.5	0.4 (0.0, 0.7), 1.8	0.1 (−0.2, 0.5), 0.5			
LCT	21, 21, 15, 15	22.6 ± 2.9	0.3 (−0.0. 0.7), 1.3	0.4 (0.0, 0.8), 1.8	0.2 (−0.2. 0.5), 0.9			
P value						0.93	<0.001	0.52
Right TSF, mm								
LD + MCT[a]	21, 21, 18, 17	10.2 ± 7.1	− 1.8 (−3.0, −0.6), −17.6	− 2.1 (−3.3, −0.8), −20.6	− 1.1 (−2.3, 0.2), −10.8			
MCT[a,b]	21, 21, 16, 16	10.1 ± 5.1	−0.6 (−1.8, 0.6), −5.9	− 1.5 (−2.7, −0.2), −14.9	− 0.9 (−2.1, 0.4), −8.9			
LCT[b]	21, 21, 15, 15	11.6 ± 5.5	0.3 (−1.0, 1.6), 2.6	1.1 (−0.3, 2.4), 9.5	1.4 (0.0, 2.7), 12.1			
P value						0.012	0.031	0.06
Left TSF, mm								
LD + MCT[a]	21, 21, 18, 17	7.5 ± 4.9	− 1.3 (−2.2, −0.3), −17.3	− 1.6 (−2.6, −0.7), −21.3	− 1.1 (−2.1, −0.2), −14.7			
MCT[a,b]	21, 21, 16, 16	7.3 ± 5.0	−0.7 (−1.7, 0.2), −9.6	− 1.1 (−2.1, −0.1), −15.1	− 0.2 (−1.2, 0.8), −2.7			
LCT[b]	21, 21, 15, 15	8.3 ± 4.9	0.5 (−0.6, 1.5), 6.0	0.8 (−0.3, 1.8), 9.6	0.8 (−0.2, 1.9), 9.6			
P value						0.012	0.06	0.46
Calculated right AMA, cm^2								
LD + MCT	21, 21, 18, 17	28.2 ± 2.7	0.8 (−1.1, 2.6), 2.8	1.2 (−0.8, 3.1), 4.3	0.4 (−1.6, 2.4), 1.4			
MCT	21, 21, 16, 16	29.4 ± 5.2	0.5 (−1.3, 2.3), 1.7	1.7 (−0.3, 3.7), 5.8	1.0 (−1.0, 3.0), 3.4			
LCT	21, 21, 15, 15	29.8 ± 3.8	0.3 (−1.7, 2.3), 1.0	− 2.0 (−4.2, 0.1), −6.7	− 2.5 (−4.7, −0.4), −8.4			
P value						0.09	0.30	0.10

(*Continued*)

TABLE 2 (*Continued*)

Measure and group	n[2]	Baseline	Change (95% CI), % change[3]			Fixed effects[4]		
			1.5-mo intervention	3-mo intervention	Washout	Group	Time	Group by time
Calculated left AMA, cm^2								
LD + MCT	21, 21, 18, 17	29.4 ± 2.7	0.4 (−1.8, 2.7), 1.4	1.1 (−1.1, 3.4), 3.7	0.4 (−1.9, 2.6), 1.4			
MCT	21, 21, 16, 16	30.6 ± 4.6	0.3 (−1.9, 2.5), 1.0	0.9 (−1.4, 3.1), 2.9	0.1 (−2.1, 2.3), 0.3			
LCT	21, 21, 15, 15	31.4 ± 4.0	− 1.2 (−3.7, 1.3), −3.8	− 1.2 (−3.8, 1.3), −3.8	− 1.6 (−4.2, 0.9), −5.1			
P value						0.47	<0.001	0.23
Right CC, cm								
LD + MCT	21, 21, 18, 17	28.5 ± 3.0	− 0.3 (−0.9, 0.2), −1.1	0.1 (−0.5, 0.7), 0.4	0.8 (0.2, 1.4), 2.8			
MCT	20, 20, 15, 15	29.5 ± 4.6	0.3 (−0.3, 0.8), 1.0	0.5 (−0.1, 1.1), 1.7	0.1 (−0.5, 0.8), 0.3			
LCT	22, 22, 15, 15	29.5 ± 3.2	− 0.5 (−1.0, 0.1), −1.7	− 0.1 (−0.8, 0.5), −0.3	− 0.2 (−0.8, 0.4), −0.7			
P value						0.21	0.10	0.09
Left CC, cm								
LD + MCT	21, 21, 18, 17	28.7 ± 3.0	− 0.0 (−0.6, 0.6), −0.0	0.4 (−0.2, 1.0), 1.4	0.8 (0.2, 1.4), 2.8			
MCT	20, 20, 15, 15	29.1 ± 4.8	0.1 (−0.4, 0.7), 0.3	0.4 (−0.3, 1.0), 1.4	0.1 (−0.5, 0.8), 0.3			
LCT	22, 22, 15, 15	29.2 ± 3.2	− 0.2 (−0.9, 0.4), −0.7	− 0.4 (−1.1, 0.3), −1.4	− 0.6 (−1.3, 0.1), −2.0			
P value						0.09	0.60	0.15

[1]Values are expressed as the mean ± SD or adjusted mean (95% CI). The adjusted mean changes in columns without a common superscript letter showed statistically significant differences between the groups, $P < 0.05$. AC, arm circumference; AMA, mid-upper-arm muscle area; CC, calf circumference; LCT, 6 g of long-chain triglycerides; LD + MCT, leucine- and cholecalciferol-enriched supplement with 6 g of medium-chain triglycerides; MCT, 6 g of medium-chain triglycerides; TSF, triceps skinfold thickness.

[2]Number of participants is shown at baseline, 1.5-mo intervention, 3-mo intervention, and washout, respectively.

[3]The value of % change = adjusted mean change from baseline/mean of baseline value × 100 is shown. This value was used to describe the degree of effect.

[4]*P* value represents the significance of the fixed effects for changes in a variable as assessed by a linear mixed model adjusted for baseline values in each measurement, age, sex, BMI, right-hand grip strength, and total FIM score.

TABLE 3 Muscle strength and function at baseline, and changes from baseline at 1.5 and 3 mo after the initiation of the intervention (intervention) and at 1.5 mo after the termination of the intervention (washout) in the LD + MCT, MCT, and LCT groups in model 2 (adjusted for each baseline value and other confounders) (intention-to-treat analysis set, $n = 64$)[1]

			Change (95% CI), % change[3]			Fixed effects[4]		
Measure and group	n[2]	Baseline	1.5-mo intervention	3-mo intervention	Washout	Group	Time	Group by time
Right-hand grip strength, kg								
LD + MCT[a]	20, 20, 17, 16	9.9 ± 3.8	0.8 (−0.1, 1.7), 8.1	2.1 (1.2, 3.1), 21.2	0.9 (−0.1, 1.8), 9.1			
MCT[a]	21, 21, 16, 16	11.9 ± 8.7	0.9 (0.0, 1.8), 7.6	2.3 (1.3, 3.2), 19.3	1.4 (0.5, 2.4), 11.8			
LCT[b]	18, 18, 14, 14	10.4 ± 5.6	−0.9 (−1.8, 0.1), −8.7	−0.2 (−1.3, 0.8), −1.9	−1.0 (−2.0, 0.1), −9.6			
P value						0.001	<0.001	0.66
Left-hand grip strength, kg								
LD + MCT	20, 20, 17, 16	10.0 ± 3.1	0.8 (0.1, 1.5), 8.0	1.4 (0.6, 2.1), 14.0	0.1 (−0.7, 0.9), 1.0			
MCT	19, 19, 14, 14	10.5 ± 4.5	0.2 (−0.5, 0.9), 1.9	1.0 (0.2, 1.8), 9.5	0.7 (−0.1, 1.5), 6.7			
LCT	18, 18, 14, 14	11.4 ± 6.2	−0.3 (−1.1, 0.5), −2.6	0.6 (−0.2, 1.5), 5.3	−0.2 (−1.1, 0.6), −1.8			
P value						0.27	0.001	0.26
Right knee extension time, s								
LD + MCT[a,b]	20, 20, 17, 16	73 ± 45	17 (3, 31), 23.3	33 (18, 48), 45.2	3 (−12, 19), 4.1			
MCT[a]	19, 19, 15, 15	60 ± 39	26 (12, 41), 43.3	39 (24, 55), 65.0	12 (−4, 28), 20.0			
LCT[b]	19, 19, 14, 14	69 ± 42	6 (−9, 20), 8.7	12 (−5, 28), 17.4	−11 (−27, 5), −15.9			
P value						0.040	<0.001	0.92
Left knee extension time, s								
LD + MCT	20, 20, 17, 16	78 ± 46	26 (12, 41), 33.3	32 (17, 47), 41.0	16 (0, 31), 20.5			
MCT	18, 18, 14, 14	69 ± 43	22 (7, 38), 31.9	33 (17, 50), 47.8	9 (−7, 25), 13.0			
LCT	19, 19, 14, 14	76 ± 44	6 (−9, 21), 7.9	8 (−8, 24), 10.5	−3 (−19, 13), −3.9			
P value						0.08	<0.001	0.74
Walking speed, m/s								
LD + MCT	17, 17, 14, 14	0.59 ± 0.33	0.02 (−0.05, 0.08), 3.4	0.07 (0.00, 0.13), 11.9	0.02 (−0.05, 0.09), 3.4			
MCT	18, 18, 14, 14	0.58 ± 0.38	0.04 (−0.02, 0.10), 6.9	0.08 (0.02, 0.15), 13.8	0.02 (−0.04, 0.09), 3.4			
LCT	15, 15, 12, 12	0.39 ± 0.28	0.01 (−0.06, 0.07), 2.6	−0.02 (−0.09, 0.05), −5.1	−0.02 (−0.09, 0.05), −5.1			
P value						0.34	0.20	0.40
Leg open and close test, n/10 s								
LD + MCT	19, 19, 16, 15	3.66 ± 1.79	1.85 (0.97, 2.72)[a], 50.5	2.70 (1.78, 3.62)[a], 73.8	1.34 (0.40, 2.27)[a,*], 36.6			
MCT	19, 19, 15, 15	4.74 ± 3.29	1.53 (0.67, 2.38)[a], 32.3	2.28 (1.37, 3.19)[a], 48.1	1.25 (0.34, 2.16)[a,*], 26.4			
LCT	19, 19, 14, 14	4.84 ± 2.74	−0.02 (−0.90, 0.86)[b], −0.4	−0.59 (−1.52, 0.35)[b], −12.2	−1.48 (−2.42, −0.54)[b], −30.6			
P value						<0.001	<0.001	0.045
Peak expiratory flow, L/min								
LD + MCT	19, 19, 16, 15	186 ± 66	4 (−16, 24), 2.2	18 (−3, 40), 9.7	3 (−19, 25), 1.6			
MCT	21, 21, 16, 16	182 ± 83	11 (−9, 30), 6.0	13 (−8, 34), 7.1	15 (−6, 36), 8.2			
LCT	19, 19, 14, 14	178 ± 62	1 (−20, 22), 0.6	−5 (−28, 17), −2.8	−21 (−43, 2), −11.8			
P value						0.21	0.37	0.41
RSST, n/30 s								
LD + MCT	19, 19, 16, 15	1.8 ± 1.0	0.3 (−0.1, 0.7), 16.7	0.8 (0.3, 1.2)[a], 44.4	0.0 (−0.4, 0.5)[a,b], 0.0			
MCT	21, 21, 16, 16	1.8 ± 1.4	0.1 (−0.3, 0.5), 5.6	0.5 (0.1, 1.0)[a], 27.8	0.5 (0.0, 0.9)[a], 27.8			
LCT	20, 20, 14, 14	1.8 ± 1.4	0.1 (−0.4, 0.5), 5.6	−0.5 (−0.9, 0.0)[b], −27.8	−0.7 (−1.2, −0.2)[b], −38.9			
P value						0.001	0.15	0.022

[1] Values are expressed as the mean ± SD or adjusted mean (95% CI). The adjusted mean changes in columns without a common superscript letter showed statistically significant differences between the groups, $P < 0.05$. Asterisks indicate a statistically significant difference compared with at 3-mo intervention within the group, $^{*}P < 0.05$ (by Bonferroni correction test). LCT, 6 g of long-chain triglycerides; LD + MCT, leucine- and cholecalciferol-enriched supplement with 6 g of medium-chain triglycerides; MCT, 6 g of medium-chain triglycerides; RSST, repetitive saliva swallowing test.

[2] Number of participants is shown at baseline, 1.5-mo intervention, 3-mo intervention, and washout, respectively.

[3] The value of % change = adjusted mean change from baseline/mean of baseline value × 100 is shown. This value was used to describe the degree of effect.

[4] *P* value represents the significance of the fixed effects for changes in a variable as assessed by a linear mixed model adjusted for baseline values in each measurement, age, sex, BMI, right-hand grip strength, and total FIM score.

TABLE 4 FIM score at baseline, and changes from baseline at 1.5 and 3 mo after the initiation of the intervention (intervention) and at 1.5 mo after the termination of the intervention (washout) in the LD + MCT, MCT, and LCT groups in model 2 (adjusted for each baseline value and other confounders) (intention-to-treat analysis set, $n = 64$)[1]

			Change (95% CI), % change[3]			Fixed effects[4]		
Measure and group	n[2]	Baseline	1.5-mo intervention	3-mo intervention	Washout	Group	Time	Group-by-time
Total FIM score (total 126 points)								
LD + MCT	21, 21, 18, 17	77.6 ± 24.8	1.0 (−2.9, 4.9)*, 1.3	6.9 (2.7, 11.1)[a], 8.9	0.9 (−3.4, 5.1)[a,*], 1.2			
MCT	21, 21, 16, 16	75.0 ± 29.3	3.8 (−0.1, 7.7), 5.1	5.6 (1.3, 9.9)[a], 7.5	− 0.5 (−4.8, 3.8)[a,*], −0.7			
LCT	22, 22, 15, 15	78.3 ± 29.8	− 2.4 (−6.6, 1.8), −3.1	− 6.6 (−11.3, −2.0)[b], −8.4	− 12.7 (−17.3, −8.1)[b], −16.2			
P value						<0.001	<0.001	0.020
Motor score (total 91 points)								
LD + MCT[a]	21, 21, 18, 17	56.6 ± 18.3	0.8 (−1.9, 3.6), 1.4	4.2 (1.2, 7.2), 7.4	0.8 (−2.3, 3.8), 1.4			
MCT[a]	21, 21, 16, 16	54.6 ± 21.9	2.5 (−0.2, 5.2), 4.6	3.4 (0.4, 6.5), 6.2	− 0.7 (−3.7, 2.4), −1.3			
LCT[b]	22, 22, 15, 15	55.1 ± 23.0	− 2.7 (−5.6, 0.3), −4.9	− 5.0 (−8.3, −1.7), −9.0	− 9.2 (−12.5, −5.9), −16.7			
P value						<0.001	<0.001	0.08
Cognitive score (total 35 points)								
LD + MCT[a]	21, 21, 18, 17	21.0 ± 7.7	0.4 (−1.3, 2.0), 1.9	2.9 (1.2, 4.7), 13.8	0.3 (−1.5, 2.1), 1.4			
MCT[a]	21, 21, 16, 16	20.6 ± 9.7	1.6 (−0.0, 3.2), 7.8	2.2 (0.4, 4.0), 10.7	0.8 (−1.1, 2.6), 3.9			
LCT[b]	22, 22, 15, 15	23.1 ± 8.5	− 1.3 (−3.1, 0.4), −5.6	− 1.8 (−3.7, 0.2), −7.8	− 3.6 (−5.6, −1.7), −15.6			
P value						0.001	0.003	0.21

[1]Values are expressed as the mean ± SD or adjusted mean (95% CI). The adjusted mean changes in columns without a common superscript letter showed statistically significant differences between the groups, $P < 0.05$. Asterisks indicate a statistically significant difference compared with at 3-mo intervention within the group, $^*P < 0.05$ (by Bonferroni correction test). FIM, Functional Independence Measure; LCT, 6 g of long-chain triglycerides; LD + MCT, leucine- and cholecalciferol-enriched supplement with 6 g of medium-chain triglycerides; MCT, 6 g of medium-chain triglycerides.

[2]Number of participants is shown at baseline, 1.5-mo intervention, 3-mo intervention, and washout, respectively.

[3]The value of % change = adjusted mean change from baseline/mean of baseline value × 100 is shown. This value was used to describe the degree of effect.

[4]P value represents the significance of the fixed effects for changes in a variable as assessed by a linear mixed model adjusted for baseline values in each measurement, age, sex, BMI, right-hand grip strength, and total FIM score.

compared because their comparisons were not meaningful due to the differential effects of time among the groups. The significance of the main effect of time was not considered in those additional analyses because the difference in overall changes (a mean of 3 groups) between the time points was not directly related to the effects of supplementation of MCTs. Significant *P* values for the main effects of time in all measurements were accompanied by significant differences in overall changes in time points between the 3-mo intervention and washout (data not shown).

Analysis of nutritional assessments during baseline, 3-mo intervention, and washout periods was conducted by the per-study protocol, in which the dropout participants were excluded, as described previously (5). The differences in changes [change value = 3-mo intervention (or washout) value – baseline value] between the groups were assessed using ANCOVA, adjusting for each baseline value as a covariate. When ANCOVA showed a significant difference, a Bonferroni correction test (posthoc test) was performed to compare the changes between groups.

Missing data (data that could not be collected at baseline and thereafter due to difficulty in performing tests) were not included in the analyses. All statistical analyses were performed using the SPSS 20.0 software program (IBM). An α level of 0.05 was used to determine statistical significance.

The percentage of relative change (% change) was calculated as follows: % change = adjusted mean of the change from the baseline value/mean of the baseline value × 100. This value was then used to describe the degree of effect. The % change is a single value and therefore has neither an SD nor requires statistical analysis. The % change of the individual subjects was not used in the analysis because their variations became very large.

Results

Participants and compliance

We enrolled 64 participants in the trial (Figure 1) (the intention-to-treat analysis set). Sixteen participants dropped out during the study: 10 participants (3 from the LD + MCT group, 4 from the MCT group, and 3 from the LCT group) were moved to other nursing homes for economic reasons, 5 participants (1 from the LD + MCT group and 4 from the LCT group) dropped out due to a loss of appetite, and one participant from the MCT group dropped out at the request of a family member. Thus, the remaining 48 participants completed the study (the per-protocol analysis set). Compliance with supplement treatment was 100%, and no side effects, including diarrhea, were reported.

Dietary intake (including supplements and oils)

The intake of energy, macronutrients, and some micronutrients at baseline and during the intervention period for each group in the per-protocol analysis set is shown in Table 1. The baseline daily intake of MCTs (8:0 + 10:0) was ∼180 mg (Table 1), which is much lower than the 6 g that was administered during the intervention. During the intervention, there was a 37-fold increase in intake of MCTs, a 5.7-fold increase in vitamin D (cholecalciferol and ergocalciferol), and small but significant increases in leucine (28%), essential amino acids (13%), thiamine (25%), and pyridoxine (30%) in the LD + MCT group. Therefore, in consideration of the doses that were administered, it was hypothesized that MCTs and cholecalciferol might be the nutrients that were responsible for the favorable effects. We also measured the groups' intake of energy, macronutrients, and some micronutrients at washout and found no significant differences in the change from baseline (data not shown).

In the analysis of habitual nutritional intake, which excluded the amounts of the supplements and oils that were administered, no differences between baseline and the intervention periods were observed in the changes of the groups' intake of energy, protein, fat, carbohydrate, sodium, or vitamins (data not shown). These data suggested that the supplement and MCTs treatment did not affect the habitual intake of energy and nutrients.

Confounders at baseline

For some measurements of muscle mass and function, there were differences in the results of the statistical analysis between model 1 (adjusted for each baseline value only) and model 2 (additionally adjusted for basal characteristics of the participants including age, sex, BMI, right-hand grip strength, and total FIM score at baseline). In model 1, fixed effects of the group were significant in the changes in the groups' right AMA ($P = 0.013$) (Supplemental Table 1) and PEF ($P = 0.030$) (Supplemental Table 2), whereas in model 2, they were not significant (right AMA, $P = 0.09$; PEF, $P = 0.21$) (Tables 2 and 3). Conversely, in model 1, the difference in right knee extension time was not significant ($P = 0.10$) (Supplemental Table 2), whereas it became significant in model 2 ($P = 0.040$) (Table 3).

However, for other measurements, there were no substantial differences in the results of the statistical analysis between model 1 and model 2, suggesting that baseline characteristics did not substantially affect the response to MCTs. The results from model 2 are described below.

Anthropometric measures

Table 2 shows the anthropometric measures at baseline and changes from baseline at 1.5 and 3 mo after initiation of the intervention (intervention) and at washout in the intention-to-treat analysis set. Fixed effects of the group in a linear mixed model were significant in the changes in the groups' right and left TSF (a marker of the subcutaneous fat tissue mass) ($P = 0.012$ for both TSFs).

Throughout the intervention and washout periods, the overall decreases (mean of 3 time points) in both the right and left TSF in the LD + MCT group were greater than the increases in the LCT group ($P < 0.05$ for both TSFs). The group-by-time interaction was not significant ($P = 0.06$ for the right TSF and $P = 0.46$ for the left TSF), suggesting that the effect of the group did not differ between the time points.

The calculated AMA (a marker of skeletal mass) reflected the change in the TSF. However, there was no significant difference in the group or the group-by-time interaction, although the AMA tended to increase after the intervention in the LD + MCT and MCT groups, whereas a decrease in AMA was observed in the LCT group. The tendencies for the right and left CCs to increase

after intervention were also observed in the LD + MCT and MCT groups.

Muscle strength and function

Muscle strength and function at baseline and changes from baseline at 1.5 and 3 mo after initiation of the intervention (intervention) and at washout are shown in Table 3. Fixed effects of the group in a linear mixed model were significant in the changes in the groups' right-hand grip strength ($P = 0.001$), right knee extension time ($P = 0.040$), 10-s leg open and close test performance ($P < 0.001$), and swallowing function (as assessed by RSST) ($P = 0.001$), whereas those of the group-by-time interaction were significant in the changes in the groups' 10-s leg open and close test performance ($P = 0.045$) and swallowing function ($P = 0.022$).

Throughout the intervention and washout periods, the overall increase (mean of 3 time points) in right-hand grip strength in the LD + MCT and MCT groups was greater than that in the LCT group ($P < 0.05$ for both groups). The group-by-time interaction was not significant ($P = 0.66$), suggesting that the effect of the group did not differ between the time points.

In addition, throughout the intervention and washout periods, the overall increase (mean of 3 time points) in right knee extension time in the MCT group was greater than that in the LCT group ($P < 0.05$). The group-by-time interaction was not significant ($P = 0.92$), suggesting that the effect of the group did not differ between the time points.

At the 3-mo intervention, the increase in the numbers of iterations (in 10 s) in the leg open and close test performed by the LD + MCT and MCT groups was greater in comparison to that of the LCT group ($P < 0.05$) [intention-to-treat adjusted means: LD + MCT 2.70 n/10 s (95% CI: 1.78, 3.62), MCT 2.28 n/10 s (1.37, 3.19), LCT −0.59 n/10 s (−1.52, 0.35); 73.8%, 48.1%, and −12.2% change from baseline, respectively]. Increases in the LD + MCT and MCT groups were attenuated at washout ($P < 0.05$ in both groups).

At the 3-mo intervention, the increase in the number of swallows (in 30 s) in the LD + MCT and MCT groups was greater than the decrease in the LCT group ($P < 0.05$) [intention-to-treat adjusted means: LD + MCT 0.8 n/30 s (95% CI: 0.3, 1.2), MCT 0.5 n/30 s (0.1, 1.0), LCT −0.5 n/30 s (−0.9, 0.0); 44.4%, 27.8%, and −27.8% change from baseline, respectively].

ADL

The FIM scores at baseline and their changes from baseline at 1.5 and 3 mo after initiation of the intervention (intervention) and at washout are shown in Table 4. Fixed effects of the group in a linear mixed model were significant in the changes in the groups' total FIM score ($P < 0.001$), the motor domain ($P < 0.001$), and the cognitive domain ($P = 0.001$), whereas that of the group-by-time interaction was significant in the changes in the groups' total FIM score ($P = 0.020$).

At the 3-mo intervention, the increase in total FIM score in the LD + MCT and MCT groups was greater than that in the LCT group ($P < 0.05$) [intention-to-treat adjusted means: LD + MCT 6.9 points (95% CI: 2.7, 11.1), MCT 5.6 points (1.3, 9.9), LCT −6.6 points (−11.3, −2.0); 8.9%, 7.5%, and −8.4% change from baseline, respectively]. Increases in the LD + MCT and MCT groups were attenuated markedly at washout ($P < 0.05$ in both groups).

Throughout the intervention and washout periods, the overall increase (mean of 3 time points) in motor and cognitive scores of the FIM in the LD + MCT and MCT groups was greater than that in the LCT group ($P < 0.05$ for both scores and both groups). The group-by-time interaction was not significant ($P = 0.08$ in motor score and $P = 0.21$ in cognitive score), suggesting that the effect of the group did not differ between the time points.

Discussion

This study, which provided a control group (LCTs only) and investigated time course changes, clearly shows that in frail elderly individuals, MCTs are an important nutrient for increasing muscle strength and function and ADL. Their increases were greater at 3 mo than at 1.5 mo after initiation of the intervention and were attenuated at the end of the 1.5-mo washout period. These data suggest that a 3-mo intervention may be required to obtain substantial effects from MCTs and that the effects are reversible.

Differences and similarities between the previous and present studies

Similarly to a previous study in a per-protocol analysis (5), the results of the present study in an intention-to-treat analysis showed that the administration of MCTs (6 g) along with a leucine- and cholecalciferol-enriched supplement for 3 mo increased the leg open and close score. This change from baseline was 68.2% in the previous study (5) and 73.8% in the present study (Table 3). However, the changes in the right AMA, right-hand grip strength, right and left leg (knee) extension time, walking speed, and PEF at the 3-mo intervention, which were significant (by ANCOVA in a 1-time point study) in the previous study (5), did not reach significance in the present study (by a linear mixed model in a 3-time point study), although the trends were similar to those of the previous study (5).

In the previous and present studies, the LD + MCT group showed greater increases in right-hand grip strength than in left-hand grip strength. In the present study, only 1 participant in the LD + MCT group was left-handed, due to paralysis of the right hand, and all others were right-handed. Thus, we hypothesized that the participants used their right hands preferentially and that this increased the right-hand muscle mass, which led to replacement of the fat mass. MCTs might be more effective for muscles that are frequently used.

Differences in the LD + MCT and MCT groups

After the 3-mo intervention, the % changes (increases) from baseline in the leg open and close test, RSST, and total FIM score in the LD + MCT group were 73.8%, 44.4%, and 8.9%, respectively, whereas those in the MCT group were 48.1%, 27.8%, and 7.5%, respectively (Tables 3 and 4). The increases were smaller in the MCT group than in the LD + MCT group; however, the differences in these increases between the LD + MCT and MCT groups were not significant by a posthoc

test (Tables 3 and 4), suggesting that most of the increases in these scores were solely due to MCTs. However, a small difference between the LD + MCT and MCT groups might be detected by increasing the number of participants. To rule out LD as a contributor that interacts specific to MCTs, comparisons of groups consuming LD + LCT and LCTs would also be required. However, in our previous study, the LD + LCT group did not improve muscle function (5).

Mechanism by which MCTs increase muscle function and the dosage of MCTs required

Activation of ghrelin by MCTs is a possible cause of the increased muscle function in response to MCTs supplementation. *O*-*n*-octanoylation (8:0) is essential for the activation of ghrelin, which stimulates the release of growth hormone (15). Thus, an increase in circulating 8:0 via portal circulation or chylomicrons may activate ghrelin, leading to an increase in growth hormone concentration, which increases muscle mass. Indeed, in humans, several studies have shown that supplementation with MCTs increased the concentration of acyl-ghrelin (active form) but did not affect that of desacyl-ghrelin (inactive form) in serum or plasma (16–18). Growth hormone and acyl-ghrelin concentrations were significantly lower in older adults compared with young adults, suggesting that supplementation with MCTs might be more effective in older adults (19).

A positive correlation was found between the amount of MCTs administered and serum acyl-ghrelin concentrations ($r = 0.44$, $P < 0.01$), and a dosage of 6 g/d for 2–6 wk was required to significantly increase the acyl-ghrelin concentration in anorexia nervosa patients (17). In cachectic patients with chronic respiratory disease, enteral administration of a 3.0-g/d dose of octanoic acid triglyceride for 2 wk could increase plasma acyl-ghrelin concentrations (16). In our preliminary trial for dose determination, a 6-g dose of oil showed good tolerability in the frail elderly adults. Therefore, the 6 g/d of MCTs administered in our study appears suitable for frail elderly individuals.

Body weight and fat-free mass

MCTs have been used as part of a program of weight loss achieved through increased energy expenditure and lipid oxidation and led to a reduction in fat mass (20, 21). However, few studies have measured the effects of MCTs on fat-free mass (FFM). The administration of 18–24 g/d MCTs for 16 wk in overweight subjects on a weight-loss diet showed greater loss of FFM (-0.93 ± 0.41 kg) than with olive oil (22). A 9.9-g/d supplementation of MCTs in a very-low-calorie diet for 4 wk in obese women showed a 2.7-kg decrease in FFM (23). However, both studies of MCTs were conducted as part of a weight-loss program and therefore did not measure the effect of MCTs oil alone. The reduction in FFM observed in these studies may be mediated by a reduction in energy intake. Supplementation of MCTs may lead to increases in muscle mass and energy expenditure and promote a reduction in fat mass.

In our study, the differences in the changes in the groups' body weight and BMI values after the 3-mo intervention were not significant by a linear mixed model (Table 2). However, increments in body weight and BMI were observed in the MCT group. The increases in muscle mass and strength in response to MCTs may lead to increases in body weight and BMI. Computed tomography or MRI studies to assess muscle mass would be required.

Limitations

The limitations of this study are as follows. *1*) The number of participants might be too small to observe significant effects of MCTs in some measures and significant differences in measures between the LD + MCT and MCT groups due to a lack of statistical power. Indeed, the actual sample size ($n = 64$) was less than that planned ($n = 87$). A large-scale intervention study or meta-analysis may clarify these issues. *2*) The examiners were not completely blinded to treatment allocation, which could bias the results. There was a chance that the examiners might favorably measure muscle functions in some groups. *3*) Because this study targeted only elderly frail Japanese individuals, we did not address whether similar favorable effects of MCTs would be observed in Western populations with a larger body size or in nonfrail subjects. More than 6 g/d of MCTs might be needed to substantially improve muscle function in these populations.

In conclusion, statistically significant improvements in major measurements of muscle strength and function were observed in the MCTs-containing groups of 2 independent studies, and ADL estimated by the FIM score, which was assessed in a double-blinded manner, was significantly improved by supplementation with MCTs relative to LCTs, strongly suggesting that supplementation with MCTs (6 g/d) is a feasible means of improving the muscle strength and function and ADL of frail elderly individuals. In addition, an increase in ADL by supplementation with MCTs might reduce the burden of the caregivers.

The authors' contributions were as follows—SA, OE, and MS: designed the research; SA and MS: conducted the research; SA and OE: analyzed the data or performed the statistical analysis; OE: wrote the manuscript; and OE has the primary responsibility for the final content; and all of the authors read and approved the final manuscript. None of the authors report a conflict of interest related to the research presented in this article.

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