

Combined Intervention of Medium-Chain Triacylglycerol Diet and Exercise Reduces Body Fat Mass and Enhances Energy Expenditure in Rats

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Summary Previous studies indicated that a medium-chain triacylglycerol (MCT) diet could inhibit body fat accumulation. It is also well established that exercise can reduce fat mass. However, the effects of a combination of MCT diet and exercise on reduction of fat mass have not been studied. Here we examined whether MCT diet and exercise intervention exert cooperative effects on body composition. Rats were assigned to 4 groups: 1. LCT diet, control (LCT-C); 2. MCT diet, control (MCT-C); 3. LCT diet, exercise (LCT-E); 4. MCT diet, exercise (MCT-E). After the 6-wk intervention, visceral fat mass was measured by CT scan and dissection, and energy expenditure was estimated for 24 h. The value of the visceral fat mass showed a significant correlation between CT scan and dissection ($r=0.995$, $p<0.001$). Visceral fat mass in the MCT-C group was lower than that in the LCT-C group. Furthermore, the fat-lowering effects were greater in the MCT-E group than that in either intervention alone. Thus significant effects of the MCT diet and exercise on the reduction of visceral fat mass were observed. Energy expenditure was significantly higher in the MCT-E group than in the other groups. Our present findings suggest that combined intervention of MCT diet and exercise has an additive effect on reduction of visceral and subcutaneous fat accumulation, and that this effect may be partially related to increased energy expenditure. However, future studies are necessary to define the relationship between energy expenditure and fat mass accumulation.

Key Words medium-chain triacylglycerols, fat mass, exercise, energy expenditure, CT scan

Medium-chain triacylglycerol (MCT) is edible oil composed of C8 and C10 saturated fatty acids. Compared with long-chain triacylglycerol (LCT), MCT has several unique physiological and biological characteristics (1, 2). Medium-chain fatty acids (MCTFA) are absorbed through the portal system without resynthesis of triacylglycerol in intestinal cells and are predominantly subjected to β -oxidation in the liver. Only a small proportion of such fatty acids is stored as fat (3). Consequently, MCT are easily oxidized, because their intramitochondrial transport does not require carnitine palmitoyltransferase (CPT), the rate-limiting enzyme of mitochondrial β -oxidation. Therefore, the digestion, absorption and metabolism of MCT differ markedly from those of LCT (4). Recently it has been reported that a MCT diet decreases the deposition of fat in adipose tissue in humans and rats (5, 6).

The accumulation of visceral fat, independent of total body fat, is associated with the development of metabolic syndrome, characterized by dyslipidemia, hypertension, glucose intolerance, and hyperinsulinemia (7–9). Therefore, it is important to reduce the visceral fat mass in order to prevent metabolic syndrome. It is well

established that exercise training is beneficial for control of body weight and fat mass (10–12), and that endurance exercise training can enhance adipocyte lipolysis in animals and humans (13, 14). Fushiki et al. (15) report an increase of swimming endurance capacity of mice with the combination of MCT diet and exhaustion exercise. However, the combined effects of MCT diet with moderate (aerobic) exercise on reduction of fat mass have not been well-defined. In this study, we examined the combined effects of a MCT diet and running exercise on visceral and subcutaneous fat mass in rats by using a CT scan. We also compared the difference between the methods of measurement of the visceral fat: by CT scan and by dissection.

MATERIALS AND METHODS

Materials. MCT (consisting of octanoate and decanoate) and LCT (rapeseed oil as a common edible oil) were prepared by The Nisshin Oillio Group, Ltd. (Tokyo, Japan). Their fatty acid compositions (Table 1) were measured by gas chromatography (6890 series; Agilent Technologies, Palo Alto, California, USA) with a capillary column (SP2340; Supelco, Bellefonte, Pennsylvania, USA).

Animals and diets. All animals were treated in accor-

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Table 1. Fatty acid compositions of test oils.¹

Fatty acid ²	LCT ³	MCT ⁴
	(g/100 g total fatty acids)	
8:0	ND ⁵	74.4
10:0	ND	25.6
16:0	4.2	ND
18:0	2.0	ND
18:1	59.6	ND
18:2(<i>n</i> -6)	20.4	ND
18:3(<i>n</i> -3)	10.2	ND
Others	3.6	ND

¹ Values determined by gas chromatography.

² Number of carbon atoms:number of double bonds.

³ Rapeseed oil.

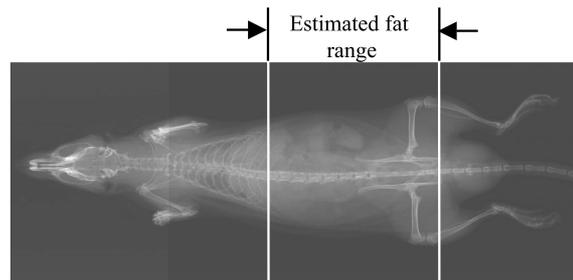
⁴ Medium chain triacylglycerols.

⁵ Not detected.

dance with the guidelines for the care and use of laboratory animals (Notification of the Prime Minister's Office in Japan). Five-week-old male Wistar rats were purchased from SLC (Hamamatsu, Japan). They were housed individually in stainless steel wire-bottom cages in a room maintained at 22–24°C with a 12-h light-dark cycle (dark period: 08:00–20:00). The food and body weight (BW) were measured in the dark-period before the running exercise. After a week of adapting to the environment, the rats were divided into the following four BW-matched groups with six rats in each group: 1. LCT diet control group (LCT-C), 2. MCT diet control group (MCT-C), 3. LCT diet and exercise group (LCT-E) and 4. MCT diet and exercise group (MCT-E). The LCT diet contained the following ingredients (g/kg): cornstarch, 479.5 (8.0 MJ); casein, 200 (3.3 MJ); sucrose, 100 (1.7 MJ); LCT, 120 (4.5 MJ); AIN-93G mineral mix, 35; AIN-93G vitamin mix (16), 10; cellulose, 50; L-cystine, 3; choline bitartrate, 2.5; and TBHQ, 0.045 (total energy:17.5 MJ). The MCT diet contained the following ingredients (g/kg): cornstarch, 504.5 (8.4 MJ); casein, 200 (3.3 MJ); sucrose, 100 (1.7 MJ); LCT, 20 (0.8 MJ); MCT, 100 (3.3 MJ); AIN-93G mineral mix, 35; AIN-93G vitamin mix, 10; cellulose, 25; L-cystine, 3; choline bitartrate, 2.5; and TBHQ, 0.045 (total energy: 17.5 MJ). We matched the lipid content with equal weight, so we corrected cornstarch and cellulose contents to match total energy. The feeding was done every day and BW was measured every week. Each group of rats were managed by the pair-fed control method. The pair-fed rats were fed an amount of food that was equal to the average amount of food consumed by the LCT-E group or by the MCT-E group in the previous feed.

Exercise protocol. The exercise regimen consisted of running 5 d/wk on a flatbed treadmill for 45 min/d at 20 m/min. The running exercise was performed between 10:00 and 12:00. To acclimate the rats to running exercise, all of the rats were run on a treadmill (Natsume Corp., Tokyo, Japan) for 3 d before the experiment. The speed of the treadmill and the duration of

A) A CT scan image of a subject.



B) A CT-scan slice at a level 40 mm below the diaphragm.

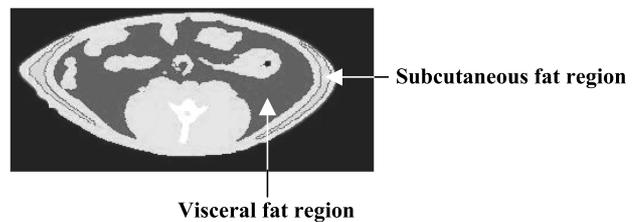


Fig. 1. CT scan image. (A) A CT scan image of a subject. Estimation of fat volumes (visceral and subcutaneous fat mass) were conducted in the abdominal region from the diaphragm to the bottom of the abdominal cavity at 2-mm CT slice intervals. (B) A CT scan slice at 40 mm below the diaphragm. The inner area is the visceral fat region, and the outer regions on each side are subcutaneous fat regions.

each running session were gradually increased from 15 m/min for 15 min to 20 m/min for 45 min. Thus, this running intensity and duration (20 m/min for 45 min) were done by the exercise groups from the beginning to the end of the study. The running regimen did not involve any form of electrical shock device. If rats stopped running they were nudged with a soft brush to encourage them to continue.

Energy expenditure. All of the rats were measured in the metabolic chamber in the 5th or 6th week of study. The rats in the exercise groups were measured on the weekend (no exercise training day). Oxygen consumption and carbon dioxide production were measured every 3 min for 24 h under resting conditions using a metabolism measuring system for small animals (MK-5000R; Muromachi Kikai, Tokyo, Japan). A reference gas (5% CO₂, 95% O₂) was used to calibrate this system. VO₂ (mL/min), VCO₂ (mL/min), RQ, gas pressures, air-flow, cage temperature, ambient air temperature, pressure, and humidity were digitized, recorded every 3 min, and averaged on an hourly basis. The system calibration was carried out at every measurement. Energy expenditure (J/min) was calculated using Weir's formula (17): $(1.106 \times VCO_2 + 3.941 \times VO_2) \times 4.186$.

CT scanning. After the 6-wk intervention, fat mass in the visceral and subcutaneous regions was estimated by X-ray CT scan (Latheta LCT-100, Aloka, Tokyo, Japan). The tube voltage of the X-ray generator was 50 kV (1 mA). Scan time was 4.5 s/slice. Rats (non-fasting) were anesthetized by intraperitoneal injection of sodium pentobarbital (50 mg/kg) and their body

Table 2. Initial and final body weights, body weight gain, food intake, feed efficiency and serum adipo-cytokines concentrations in each group.¹

	LCT-C	MCT-C	LCT-E	MCT-E	<i>p</i> -values ²		
					MCT	Ex ⁴	MCT×Ex
Initial body weight (g)	130.0±1.3	129.8±1.4	130.1±1.3	130.1±1.3	0.655	0.670	0.786
Final body weight (g)	275.4±3.4	267.2±3.9	259.9±5.5 ^a	256.2±3.7 ^b	0.163	0.004	0.568
Body weight gain (g/6 wk)	135.8±4.1	130.1±1.6 ^a	129.1±4.5 ^a	127.2±4.0	0.230	0.001	0.506
Food Intake (g/6 wk)	574.0±7.9	584.2±5.9	557.1±12.2	567.7±9.4	0.267	0.084	0.980
Feed Efficiency (%) ³	25.2±0.3	23.4±0.7 ^a	23.2±0.6 ^a	22.4±0.5	0.034	0.050	0.467
Adiponectin (μg/L)	3.27±0.3	4.22±0.3 ^a	2.99±0.1	4.12±0.3 ^c	<0.001	0.242	0.989
Leptin (μg/L)	3.77±0.4	3.88±0.4	2.46±0.3 ^a	1.78±0.1 ^b	0.140	<0.001	0.260

¹ Value are means±SE, *n*=6. ^aSignificantly different from LCT-C group; ^bsignificantly different from MCT-C group; ^csignificantly different from LCT-E group (*p*<0.05).

² Significant main effects of MCT and Ex were determined by two-way ANOVA.

³ Body weight gain (g/6 wk)/food intake (g/6 wk)×100(%).

⁴ Ex: exercise.

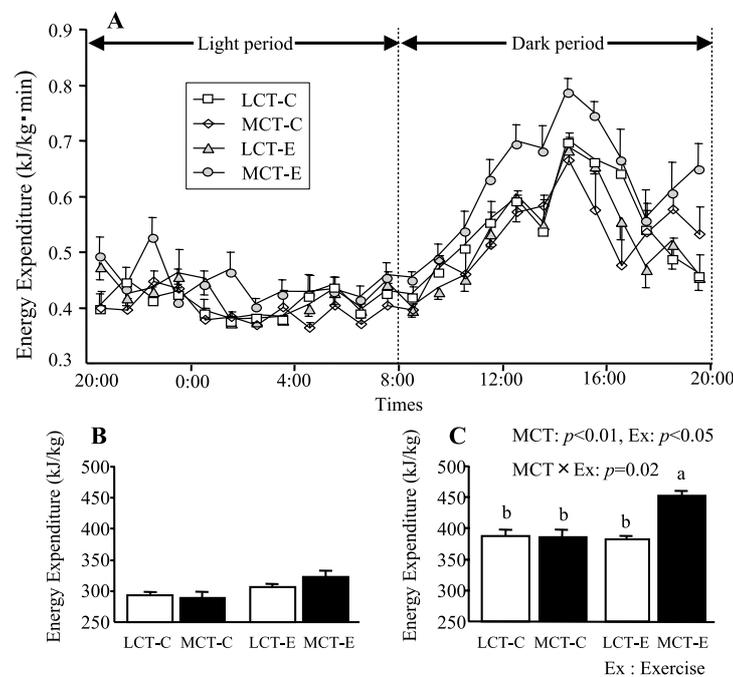


Fig. 2. Energy expenditure over 24 h measured by metabolic chamber. All of the rats were placed in the metabolic chamber for 24-h respiratory gas analysis. Oxygen consumption and carbon dioxide production were measured, and the energy expenditure was calculated from these values. (A) Data of energy expenditure over 24 h for each group. (B) Total of energy expenditure during the light period (20:00–8:00). (C) Total of energy expenditure during the dark period (8:00–20:00). Data are means±SE for 6 rats in each group. The main effects of MCT diet and exercise interventions, and their interaction were analyzed by two-way ANOVA. There were significant effects of MCT diet (*p*<0.01), exercise (*p*<0.05), and their interaction (*p*=0.02). Bars with different letters are significantly different (*p*<0.05).

weights were measured at 10:00. The anesthetized rats were placed in the CT scanner and their whole body was scanned along the body axis at 2-mm intervals. Fat volumes were measured using this device according to the manufacturer's protocol (Latheta software version 1.00). Contiguous 2-mm slice images between the diaphragm and the bottom of the abdominal cavity were used for quantitation of visceral and subcutaneous fat volumes (Fig. 1A). CT-image was displayed at 40 mm below the diaphragm (Fig. 1B).

Survey of visceral fat mass by dissection. The rats

which were CT scanned were euthanized by exsanguination under anesthesia. Fat pads from three visceral regions, that is the epididymal, perirenal (including retroperitoneal fat mass) and mesenteric (including omental fat mass), were carefully removed.

Serum adipo-cytokines. Serum was obtained by centrifuging at 300×*g* for 15 min at 4°C and frozen at −20°C. The serum adiponectin and leptin concentrations were measured by ELISA kits (Otsuka, Tokyo, and Morinaga, Yokohama, Japan, respectively) in accordance with the manufacturers' instructions. For the

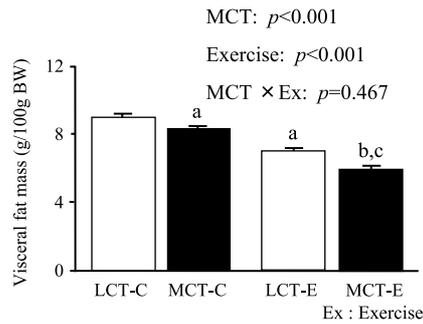


Fig. 3. CT scan data of visceral fat mass. Fat mass in the visceral region was estimated by X-ray CT scan. Data are means \pm SE for 6 rats in each group. The main effects of MCT diet and exercise, and their interaction were analyzed by two-way ANOVA. There were significant effects of MCT diet ($p<0.001$), and exercise interventions ($p<0.001$). There was no significant interaction between the two interventions. Bars with different letters are significantly different ($p<0.05$). a, Significantly different from LCT-C group; b, significantly different from MCT-C group; c, significantly different from LCT-E group ($p<0.05$).

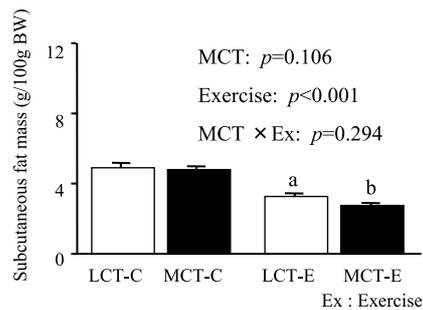


Fig. 4. CT scan data of subcutaneous fat mass. The fat mass in the subcutaneous region was estimated by X-ray CT scan. Data are means \pm SE for 6 rats in each group. The main effects of MCT diet and exercise, and their interaction were analyzed by two-way ANOVA. There was a significant effect of exercise intervention ($p<0.001$). There was no significant interaction between the MCT diet and exercise intervention. Bars with different letters are significantly different ($p<0.05$). a, Significantly different from LCT-C group; b, significantly different from MCT-C group ($p<0.05$).

absorbance measurement, we used a plate reader (Power Wave X340; Bio-Tek Instruments, Vermont, USA).

Statistical analysis. Data are expressed as means \pm SE. The main effects of the MCT diet and exercise, and interaction of the two interventions, were analyzed by two-way ANOVA (SPSS version 13-J; SPSS, Tokyo, Japan). When the significant interaction effect was detected, the significance of differences among the different groups were determined by one-way ANOVA followed by Fisher's protected least-significant-difference test. Pearson correlation was used to determine associations between CT scan and dissection data. Differences were considered significant at a level of $p<0.05$.

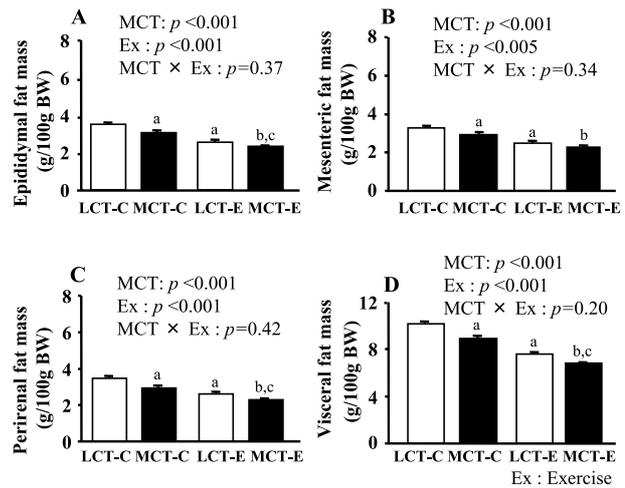


Fig. 5. Dissection data of visceral fat mass. (A) Epididymal fat mass, (B) mesenteric fat mass, (C) perirenal fat mass, and (D) visceral fat mass (the sum of the regions of the epididymal, mesenteric, and perirenal fat mass). Rats were divided into LCT-C, MCT-C, LCT-E, and MCT-E groups. Data are means \pm SE for 6 rats in each group. The main effects of MCT diet and exercise, and their interaction were analyzed by two-way ANOVA. There was a significant effect of MCT diet on the each region's, and total visceral fat mass (epididymal, $p<0.001$; mesenteric, $p<0.005$; perirenal, $p<0.001$; visceral, $p<0.001$). There was a significant effect of exercise on the each region's, and total visceral fat mass (epididymal, $p<0.001$; mesenteric, $p<0.001$; perirenal, $p<0.001$; visceral, $p<0.001$). There was no significant interaction between the MCT diet and exercise. Bars with different letters are significantly different ($p<0.05$). a, Significantly different from LCT-C group; b, significantly different from MCT-C group; c, significantly different from LCT-E group ($p<0.05$).

RESULTS

Food intake and body mass

Food intake did not differ among the four groups. Food efficiency in LCT-C rats was greater than the other three groups (Table 2). The final body weight and body weight gain were significantly lower in the exercise groups (LCT-E, MCT-E) than the control groups (LCT-C, MCT-C).

Energy expenditure over 24 h

Each group tended to exhibit higher energy expenditure during the dark period (08:00–20:00) than in the light period (20:00–08:00). Significant effects of the MCT diet ($p<0.05$) and exercise ($p<0.05$) can be seen in the increase of the energy expenditure during the dark period. There was also significant ($p=0.017$) interaction between the MCT diet and exercise. The MCT-E group exhibited significantly ($p<0.05$) higher energy expenditure than the other three groups (Fig. 2).

Effects of MCT diet and exercise on fat mass measured by CT scan

Significant effects of the MCT diet ($p<0.001$) and exercise ($p<0.001$) can be seen in the reduction of visceral fat mass (Fig. 3). The value of visceral fat was lower in the MCT-C group than in the LCT-C group.

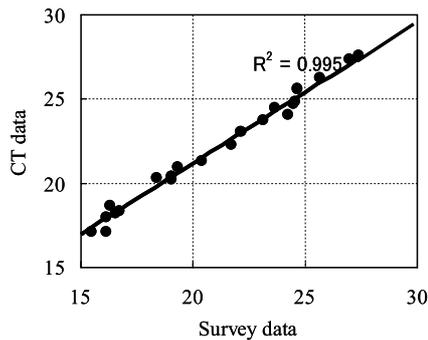


Fig. 6. Linearity of CT data and survey data. The correlation coefficients (Pearson's product-moment correlation coefficient) of the visceral fat mass data were obtained by both CT ($n=24$) and dissection ($n=24$).

Furthermore, the visceral fat was lower in the MCT-E group than in either group alone. There was a significant effect of exercise ($p<0.001$) on the reduction of subcutaneous fat mass (Fig. 4). However, no interaction was observed between the MCT diet and exercise interventions.

Effects of MCT diet and exercise on fat mass measured by dissection

The visceral fat mass, which includes the epididymal (Fig. 5A), mesenteric (Fig. 5B), and perirenal (Fig. 5C) regions, were measured. There were significant effects of exercise on each region (epididymal, $p<0.001$; mesenteric, $p<0.001$; perirenal, $p<0.001$). Similarly, there were significant effects of the MCT diet on each region (epididymal, $p<0.001$; mesenteric, $p<0.005$; perirenal, $p<0.001$). In addition, there were significant effects of the MCT diet ($p<0.001$) and exercise intervention ($p<0.001$) on reduction of the visceral fat mass (Fig. 5D). However, there was no significant interaction between the MCT diet and exercise interventions.

Correlations between the visceral fat measured by CT scan and dissection

The visceral fat mass obtained by CT scan (Fig. 3) and by dissection (sum of epididymal, mesenteric and perirenal regions, Fig. 5D) were significantly correlated ($r=0.995$, $p<0.001$) (Fig. 6).

Serum adipo-cytokines data

The serum adiponectin concentration was higher in the MCT diet groups than in the LCT diet groups. However, the serum leptin concentration was lower in the exercise groups than in the control groups (Table 2).

DISCUSSION

The novel findings of this study are as follows: 1) Compared with the LCT control diet in rats, the MCT diet reduced the accumulation of visceral fat mass; 2) The combined intervention of MCT diet and exercise showed an additive effect on reduction of fat mass accumulation, and this effect may be related to increased energy expenditure.

It is known that, compared with LCT diets, an MCT has a faster rate of oxidation that can increase the energy expenditure and diet-induced thermogenesis (DIT) (18). These biological characteristics of MCT may

contribute to fat-lowering effects. On the other hand, it has been documented that exercise training can enhance the lipolysis of adipose tissue by increasing fat oxidation and fatty acid availability (13, 14). Based on the efficacy of each MCT diet and exercise training, we hypothesized that combined intervention would result in maximizing the potential for preventing accumulation of fat mass. As we expected, a pronounced and additive effect of the two interventions was observed. We presume that exercise can enhance the β -oxidation and availability of MCEFA. Furthermore, it is likely that the exercise may increase lipolysis of adipose, mediated by β -adrenergic stimulation (19). In our study, we estimated 24-h energy expenditure, which is considered relevant to body composition. The combined interventions of MCT diet and exercise significantly enhanced the energy expenditure during the dark period (active period), but not during the light period. However, either intervention alone did not affect the energy expenditure. This result does not sufficiently reflect our body fat accumulation data, and therefore a future study should be designed to clarify the relationship between energy expenditure and fat mass accumulation.

Adipose tissue not only stores excess energy in the form of fat, but also releases physiologically active mediators known as adipo-cytokines, such as leptin and adiponectin (20). Recently, the adipo-cytokines have demonstrated links between obesity and insulin resistance in rodents and humans (21, 22). In this study, we found a significant effect of MCT diet on the increase of serum adiponectin levels. However, exercise had no effect on serum adiponectin levels. This result is similar to Bhattacharya et al.'s (23) findings which reported that exercise alone did not increase serum adiponectin levels. In a previous study (24), a rise of serum adiponectin level by MCT diet was confirmed. In that study, mRNA levels related to adiponectin gene expression were also raised. Retinoid X receptor (RXR) and peroxisome proliferators-activated receptor γ (PPAR γ) mRNA levels were significantly higher in the rats fed with MCT. These results suggest that improved glucose tolerance in rats fed with MCT may be ascribed to higher serum adiponectin level (24). Regarding the leptin, the significant main effect on decreasing the circulating level was found in exercise intervention only. However, the combined intervention of MCT diet and exercise showed a trend for a greater effect on regulation of serum adipo-cytokines than either one alone.

Recently, dual-energy X-ray absorptiometry (DXA) and X-ray computed tomography (CT) scan have been used for determining *in vivo* body composition in humans, as well as in experimental animals (25). In this study, we found a linear relationship of the visceral fat mass measured between CT scan and dissection. Nagy and Clair (26) reported that DXA-derived data tend to overestimate carcass fat mass in rat. Instead of using the DXA (2-Dimension), we tried the CT-scan (3-Dimension) for estimating fat mass in this study. Because every contiguous 2-mm CT-scanned slice was estimated in the abdominal region, fat mass was not

overestimated. Therefore, we suggest that the CT-scan can be used to more accurately predict body composition.

In conclusion, we observed that combined intervention employing MCT diet and exercise had an additive effect in preventing body fat accumulation, especially in the visceral region, and that these effects may be related to increased energy expenditure. Further studies are necessary to define the detailed mechanism of interaction between exercise and MCT diet to reduce visceral adipose tissue.

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