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The Time Course Effects of Conjugated Linoleic Acids on Body Weight, Adipose Depots and Lipid Profiles in the Male ICR Mice Fed Different Fat Sources*

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This study examined the time course effects of conjugated linoleic acid (CLA) on the body weight, adipose depots and lipid profiles of ICR male mice using two different sources of fats in the diet. Ninety eight mice weighing 25 to 30 g were divided into four groups: beef tallow (BT) and fish oil (FO), beef tallow with CLA supplementation (BTC), and fish oil with CLA supplementation (FOC) group. Eight to nine mice in each group were fed with the experimental diets for 1, 2 or 4 weeks, respectively. All mice were fed experimental diets containing 12% of total dietary fat (w/w) with or without 0.5% CLA (w/w). CLA supplementation did not affect the body weight. The weight of epididymal and visceral fats were significantly lower in BTC compared to those in BT groups during the periods examined ($p<0.05$), whereas they were significantly lower in FOC than those in FO only at 4 weeks ($p<0.05$). The levels of triglycerides in the plasma were significantly decreased in the BTC group than in BT group throughout the experimental periods ($p<0.05$). But, FOC was only effective at 4 weeks as compared to FO. The levels of total cholesterol and HDL-C were significantly increased in the BTC than in BT during the entire period ($p<0.05$), whereas there were no difference between FO and FOC on the levelsof total cholesterol and HDL-C. The levels of free fatty acids (FFA) were significantly decreased in BTC than in BT at 1 and 4weeks and in FOC only at 4 weeks as compared to FO ($p<0.05$). Taken these results together, CLA was more effective in the beef tallow diet in lowering the epididymal and visceral fat weights and triglyceride level rather than fish oil diet with CLA. Furthermore, the effect became clearer at 4 weeks than at one week of the experiment.

Key words: CLA, Body weight, Adipose depot, Lipid profile

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INTRODUCTION

Conjugated linoleic acid (CLA) is a collective name for the mixture of positional and geometric isomers of linoleic acid (*cis-9, cis-12* octadienoic acid) and has been reported to exert various beneficial effects. CLA has been reported to reduce body weight in humans,[1] pigs,[2] mice,[3-7] rats[8,9] and broilers.[10] However, it has been also observed that CLA gives no effect on body weight.[11-14] Proposed anti-obesity mechanism of CLA includes decreased food intake[4] and increased energy expenditure,[5] decreased preadipocyte differentiation and proliferation,[15] decreased lipogenesis and increased lipolysis and fat oxidation.[8]

The effects of CLA on body weight appear to depend on the types of fat used. Thus, there was a decrease in the body weight in animals fed with CLA-supplemented corn oil diet,[3,4] whereas no effect was found in the body weight of animals fed with CLA-supplemented fish oil or beef tallow.[12,14] Further supported by these reports, it has been previously proposed that CLA may influence fat deposition depending on not only the duration of the supplementary diet but also the different regions of adipose tissue in the body.[5,16]

In addition, CLA decreased plasma lipid levels and reduced the development of atherosclerosis in rabbits,[17] rats[13,18] and hamsters.[19,20] It was suggested that CLA lead to inhibition of atherosclerosis-inducing factor(s).

We investigated the time course effects of CLA supplement in the diets containing two different sources of fats (fish oil, FO and beef tallow, BT) on body weight and adipose depots in ICR male mice. Also, potentially

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hypocholesterolemic effects of CLA on plasma lipid profiles were determined.

MATERIALS AND METHODS

1. Experimental Design

Ninety eight ICR male mice aged 4 weeks were adapted with chow diet for one week. They were randomly divided into 4 groups, beef tallow (BT), and BT supplemented with 0.5% CLA (BTC), fish oil (FO) and FO supplemented with 0.5% CLA (FOC). Eight to nine mice in each group were fed with the experimental diets for 1, 2 or 4 weeks, respectively.

2. Experimental Diets

The experimental diets were composed of 59.2% carbohydrates, 19.7% proteins and 21.9% fat (12% w/w) in terms of their contribution to total calories and other nutrients were identical (Table 1). Table 2 showed the fatty acid composition in dietary oil. The two sources of dietary fat were beef tallow (BT), containing saturated fatty acids and fish oil (FO) containing docosahexaenoic acid (DHA), an n-3 fatty acid. The CLA (Natural ASA, Norway) was added to the diets of the CLA supplementation groups at 0.5% (w/w).[8] The purity of CLA was 80% and the CLA product contained 50% *cis-9, trans-11* and 50% of *trans-10, cis-12* CLA. As both beef tallow and fish oil are lacking in essential fatty acids, soy bean oil which is rich in n-6 linoleic acid was added. In order to prevent the oxidation of the fish oil, Dl-α-tocopherol (145.6 mg/100 g oil) was added to the fish oil diets. The animals were kept under 12 hour dark and light cycle conditions. Food and water were given *ad libitum*. Body weights were measured at the same designated time once a week.

Table 1. Diet composition of experimental groups

Ingredient(g)	BT	BTC	FO	FOC
Corn starch	384.635	384.635	384.635	384.635
Casein	200.054	200.054	200.054	200.054
Dextrinized cornstarch	127.745	127.745	127.745	127.745
Sucrose	96.798	96.789	96.798	96.789
Beef tallow	72.497	66.247	0	0
Fish oil	0	0	72.497	66.247
CLA[1]	0	6.25	0	6.25
Soybean oil	17.752	17.752	17.752	17.752
Fiber	50	50	50	50
Mineral mix[2]	35	35	35	35
Vitamin mix[3]	10	10	10	10
L-Cysteine	3.005	3.005	3.005	3.005
Choline bitartate	2.5	2.5	2.5	2.5
Tert-butylhydroquinone	0.014	0.014	0.014	0.014
Total(g)	1000	1000	1000	1000

1) CLA rich oil contained 80% of total conjugated linoleic acid (50% c9t11, 50% t10c12)
2) AIN 93 Mineral mixture
3) AIN 93 Vitamin mixture
BT: beef tallow, BTC: beef tallow with 0.5% CLA supplementation
FO: fish oil, FOC: fish oil with 0.5% CLA supplementation

Table 2. Fatty acid composition of dietary oil

(g/100 g oil)

Fatty acid	Beef tallow[1,5]	Soybean oil	Fish oil[2,3]	CLA[4]
14:0	3.14	0.10	2.58	-
14:1	1.17	-	-	2.00
16:0	23.57	11.00	16.48	-
16:1	4.08	0.10	4.74	-
17:0	1.64	-	-	-
17:1	1.01	-	-	-
18:0	17.99	4.00	4.14	1.00
18:1	42.97	23.40	10.94	11.00
18:2	2.74	53.20	1.08	6.00
18:3	-	7.80	2.19	-
CLA	-	-	-	80.00
20:0	1.15	0.30	1.56	-
20:1	-	-	0.36	-
20:5	-	-	5.47	-
22:6	-	-	27.65	-
Unknown	0.60	0.10	22.81	-
Total	100.00	100.00	100.00	100.00
SFA	47.49	15.40	24.76	1.00
MUFA	49.23	23.50	16.04	13.00
PUFA	2.74	61.10	36.39	86.00
S/M/P	1.0:1.04:0.06	1.0:1.53:3.98	1.0:0.65:1.47	1.0:13.0:86.00
PI	15.05	74.68	169.60	89.25

1) Supplemented 54.55mg dl-α-tocophherol/100g oil
2) Supplenmented 145.46mg dl-α-tocophherol/100g oil, Tuna oil
3) Supplemented with 4800IUvitamen A per 15g oil
4) CLA rich oil contained 80% of total conjugated linoleic acid (50% c9t11, 50% t10c12).
S/M/P: Saturated/ Monounsaturated/ Polyunsaturated fatty acid ratio
PI: Peroxidizavility index [monoenoic aicd (%)×0.25+dienoic acid (%)×1+trienoic acid (%)×2+tetraenoic acid (%)×3+pentaenoic acid(%)×4+hexaenoic acid (%)×5]

3. Sample Collections

At the end of experimental periods (1, 2 and 4 weeks), animals were fasted for 12 h before the sacrifice and anaesthetized with ethyl ether prior to being guillotined. The blood was collected in heparinized glass tubes and immediately centrifuged at 800 × g for 15 min at 4 ℃. The collected plasma was stored at -70 ℃ until use for subsequent lipid analysis. The visceral and epididymal fat pads were removed and washed in saline solution (0.9% NaCl). After the solution was blotted dry, the fat depots were weighed.

4. Biochemical Analysis

The measurements of total cholesterol (TC), HDL-Chol, and triglycerides (TG) were done by using a kit provided by Young Dong Pharmaceutical Company. Free fatty acids were also analyzed by using NEFA kit (Youngyeon Chemical Co, Tokyo, Japan).

5. Statistical Analysis

All the results were analysed by using the general linear model (GLM) from Statistic Analysis System (SAS) program. Duncan's multiple range test was used to determine the statistical differences among the experimental group at $p<0.05$. All results were expressed by mean±standard deviation (SD). The correlations between the parameters were tested by Pearson's correlation coefficient.

RESULTS

1. Food intakes and Body Weight Gain

Food intakes and body weights in mice in four experimental groups (BT, BTC, FO and FOC) for 1, 2 and 4 weeks of experiments were presented in Table 3. At one week, it was found that food intake was similar in BT and BTC groups, whereas it was significantly higher in FOC than that in FO. However, there was no significant difference in the food intakes at the rest of periods (2 and 4 weeks). Meanwhile, body weight was not significantly different among all groups at different periods of experiment.

Table 3. Effect of CLA on food intakes and weight gain in mice

		1 week	2 weeks	4 weeks
Food intakes (g)	BT	6.0±0.5^{ab}	5.9±0.6^{NS}	5.2±0.5^{NS}
	BTC	5.9±1.6^{ab}	6.0±1.2	5.3±1.3
	FO	5.3±0.3^{b}	6.5±1.2	5.6±0.6
	FOC	6.4±0.4^{a}	6.4±0.6	5.8±2.3
Weight gain (g)	BT	3.4±2.2^{NS}	5.3±2.7^{NS}	9.9±3.3^{NS}
	BTC	2.7±1.6	6.7±1.7	8.6±4.1
	FO	2.4±2.3	7.1±1.8	10.6±2.6
	FOC	4.2±1.8	6.3±1.8	8.6±2.7

BT: beef tallow, BTC: beef tallow with 0.5% CLA supplementation
FO: fish oil, FOC: fish oil with 0.5% CLA supplementation
Values are mean±S.D.
Numbers of mice in each group: 8-9
Values sharing common superscripts in the same column are not significantly different at $p<0.05$
NS: not significant

2. Adipose Depot Weights

Significant decreases in the levels of both epididymal and visceral adipose weight were found in BTC compared with those in BT at 1, 2 and 4 weeks, and in the level of epididymal fat pads weight in FOC compared with those in FO only at 4 weeks, respectively ($p<0.05$) (Table 4). The level of visceral adipose weights was significantly lower in FOC compared with those in FO at both 2 and 4 weeks of experimental periods ($p<0.05$).

Table 4. Effects of CLA on epididymal fat and visceral fat weights in mice

(g/10 g BW)

		1 week	2 weeks	4 weeks
Epididymal fat(g)	BT	0.442±0.189^{a}	0.569±0.180^{a}	0.884±0.337^{a}
	BTC	0.266±0.054^{b}	0.265±0.095^{b}	0.221±0.142^{b}
	FO	0.405±0.103^{a}	0.551±0.174^{a}	0.808±0.204^{a}
	FOC	0.378±0.040^{ab}	0.552±0.164^{a}	0.446±0.243^{b}
Visceral fat(g)	BT	0.088±0.038^{a}	0.104±0.060^{ab}	0.179±0.083^{a}
	BTC	0.032±0.021^{b}	0.039±0.022^{c}	0.039±0.032^{b}
	FO	0.097±0.037^{a}	0.133±0.050^{a}	0.195±0.092^{a}
	FOC	0.084±0.025^{a}	0.077±0.036^{bc}	0.052±0.046^{b}

BT: beef tallow, BTC: beef tallow with 0.5% CLA supplementation
FO: fish oil, FOC: fish oil with 0.5% CLA supplementation
Values are mean±S.D.
Numbers of mice in each group: 8-9
Values sharing common superscripts in the same column are not significantly different at $p<0.05$

3. Lipid Profiles in Plasma

Plasma TC, HDL-C, TG and Free fatty acid of mice are shown in Table 5. In the total Chol level, there was

Table 5. Effects of CLA on plasma lipid profile in mice

		1 week	2 weeks	4 weeks
Total -Cholesterol (mg/dl)	BT	135.8±26.9^{ab}	136.0±23.5^{b}	151.7±137.1^{b}
	BTC	158.7±32.3^{a}	178.5±25.9^{a}	204.6±27.9^{a}
	FO	115.7±13.6^{b}	104.6±15.2^{c}	110.6±11.4^{c}
	FOC	137.1±21.6^{ab}	109.3±11.0^{c}	121.2±19.1^{c}
HDL -Cholesterol (mg/dl)	BT	83.0±27.8^{a}	79.6±16.7^{b}	98.2±27.5^{b}
	BTC	91.1±20.0^{a}	114.7±29.1^{a}	131.1±27.8^{a}
	FO	63.3±9.8^{b}	67.0±12.5^{b}	72.6±7.9^{b}
	FOC	72.5±6.0^{ab}	69.5±14.5^{b}	83.7±27.5^{b}
Triglyceride (mg/dl)	BT	147.1±55.8^{a}	99.8±39.3^{a}	120.7±42.2^{a}
	BTC	101.4±55.0^{b}	52.7±36.9^{b}	58.3±39.2^{b}
	FO	80.3±22.1^{b}	63.0±18.5^{b}	92.6±25.4^{a}
	FOC	66.1±25.8^{b}	64.1±28.7^{b}	49.7±21.3^{b}
Free fatty acid (μEq/L)	BT	1866.5±393.1^{a}	1044.3±317.3^{NS}	1246.4±143.7^{a}
	BTC	1130.1±443.3^{b}	865.1±355.0	671.5±190.0^{c}
	FO	999.2±248.3^{bc}	879.9±182.8	937.4±175.1^{b}
	FOC	952.2±275.4^{c}	817.6±196.5	548.9±118.7^{c}
AI	BT	1.70±0.34^{NS}	1.72±0.22^{NS}	1.56±0.11^{NS}
	BTC	1.76±0.22	1.60±0.24	1.59±0.18
	FO	1.85±0.22	1.58±0.22	1.53±0.14
	FOC	1.89±0.19	1.61±0.24	1.52±0.32

BT: beef tallow, BTC: beef tallow with 0.5% CLA supplementation
FO: fish oil, FOC: fish oil with 0.5% CLA supplementation
Values are mean±S.D.
Numbers of mice in each group: 8-9
Values sharing common superscripts in the same column are not significantly different at $p<0.05$
NS : not significant
HDL-chol : High density lipoprotein cholesterol
AI: Atherosclerotic index. T-Chol/HDL-C

no difference between the two sources of fats. However, the levels of Chol were significantly decreased in FO than that in BT at both 2 and 4 weeks ($p<0.05$). It was also found that the level of HDL-Chol was significantly increased in BTC than that in BT at both 2 and 4 weeks ($p<0.05$). A similar increasing trend was also found in FOC compared with FO although no significant difference was found.

When the concentrations of TG were compared between BT and FO groups, significantly higher levels of the TG were found in BT group ($p<0.05$). Also, significantly decreased levels of the TG were found in BTC compared to BT at 1, 2 and 4 weeks and FOC compared to FO only at 4 weeks ($p<0.05$).

There were increased trends in the levels of free fatty acids in BT rather than FO groups, whereas significant decreases were found in both CLA-supplemented groups, BTC and FOC, only at 4 weeks ($p<0.05$).

DISCUSSION

1. The Effects of CLA on the Weights of Body and Fat Depositions

The measurements in the present study involved time courses effects of CLA supplementation with beef tallow or fish oil diet on changes in body weight, adipose depots and plasma lipid profiles in mice.

Our study showed 0.5% CLA supplement did not affect the food intake and body weight regardless of fat sources (Table 3). According to Park *et al.*[3] there was a significant 57~60% of decrease in the body fat weight although no decrease was found in the body weight in mice fed with 0.5% CLA-supplemented diet containing 5% corn oil for 4 weeks. They suggested that the decrease in the body fat weight was due to the increased β-oxidation of fatty acids. In another *in vitro* study, it was hypothesized that CLA added to a medium with bovine serum albumin, decreased lipoprotein lipase (LPL) activity, leading to decreasing fat accumulation.[15]

Similarly, West *et al.*[4] reported that there were significant decreases in the levels of body weight and total fat contents only in mice fed with 1.0 or 1.2% CLA-supplemented diets for 6 weeks regardless of low or high fat diets. They suggested that the lower intake may responsible for the less accumulation of body fat in CLA-supplemented diets. Delany *et al.*[5] found that there was a decrease in body fat with no change in the food intake in mice.

As described above, there is no general agreement on the effects of CLA on the body weight in mice. Furthermore, there were reports showing lower body weights in mice fed fish oil rather than beef tallow,[21,22] whereas other reports showed that the type of fat had no effect on the body weight.[12] However, while many studies used largely corn oil or low fat diets as fat sources, we used 21.9% fat of total calories as well as fish oil containing highly unsaturated fatty acids and beef tallow containing highly saturated fatty acids. Such different dietary sources and compositions of fats may be one of many factors to explain our results that showed no difference in the body weight in mice fed CLA-supplemented diets. A similar result was also found in the report that showed no difference in the body weight of mice fed with CLA-supplemented diet containing fish oil.[14]

How could no alteration in the body weight be explained in mice fed with CLA supplement? Hargrave *et al.*[14] reported it was possible that the desaturated and elongated isomers of CLA were responsible for the changes in the body composition. CLA may influence body fatness by competing for enzymes involved in essential fatty acid metabolism.

Another factor may also be taken into consideration and that is the ratio of active CLA isomer forms. For example, while no influence was found in the body weight regardless of the ratios of CLA isomers in the supplementary CLA mixture,[16,23,24] only the (t10c12) CLA isomer decreased the body weight. In particular, higher ratio of the isomer than other isomers in the t10c12 CLA mixture was responsible for the decrease in the body weight. The commercial CLA mixture we used consisted of 50% (c9t11) and 50% (t10c12) CLA. This may be considered as an explanation to the body weight of mice supplemented with the CLA mixture in our study.

It was further shown that the body weight was decreased while the weight of cumulative adipose depot was reduced at 4 weeks afterwards when 1% CLA supplement was used in high fat diet in AKR mice.[4] The retroperitoneal depot was reduced after 2 weeks, the inguinal and epididymal after 4 weeks and the mesenteric after 6 weeks. In our study, there was no alteration in the body weight during 4 weeks when 0.5% CLA was supplemented. However, the weights of the epididymal and visceral fats were decreased in both BTC and FOC groups fed with 0.5% CLA at 4 weeks ($p<0.05$), respectively. Several researchers[4,13] observed different effects of CLA on body weights and other tissues, and the weight of retroperitoneal depot was most sensitive to CLA. In the

present study, there was also more decreases were found in the visceral than in the epididymal fats, in particular, at 4 weeks (Table 4). Thus, in both others and our study, the decrease of the visceral fat was accompanied with no change in the body weight.

Haug *et al.*[25] suggested that the decreased LPL activity in the fat tissues was due to the lower substrate concentration caused by decreased synthesis and secretion of triglycerides (TG) in the liver when fish oil was fed. Park *et al.*[3] also suggested that the reduced serum TG might be related to CLA supplementation, which enhanced fatty acid β -oxidation in skeletal muscles and fat pads. Similarly, the reduced plasma TG in our study may be associated with the reduced weight of adipose depot. For example, the levels of TG were significantly higher in BT than those in FO at 1, 2, and 4 weeks ($p<0.05$) (Table 5). CLA supplement caused significant decreases in the levels of TG in BTC rather than BT at 1, 2 and 4 weeks and FOC rather than FO at 1 and 4 weeks ($p<0.05$), respectively. The result suggests that CLA would exert its effects on saturated rather than unsaturated fatty acids. Previous study showed that the level of free fatty acids was increased in the plasma by the entrance of more triglycerides derived from the increased body fat.[12] In accordance with the suggestion, it was noticed in our study, particularly at 4 weeks, that higher the TG concentration, higher the concentration of free fatty acids in the plasma, and more epididymal and visceral fats, and higher the concentration of free fatty acids were observed.

2. The Effects of CLA on the Plasma Lipid Profiles

The levels of plasma TC and LDL-Chol, as risk factors of arthrosclerosis were demonstrated to increase or decrease by the diets containing high levels of saturated and unsaturated fatty acids, respectively.[26] It is known that fish oil containing high level of n-3 fatty acids decreases VLDL and LDL synthesis through inhibiting apoprotein B synthesis, and that larger space is required for loading unsaturated fatty acids in the LDL molecules, thus leading to less TC contents in LDL.[27,28] In our study, TC levels were significantly higher in BT than those in FO at 1, 2 and 4 weeks ($p<0.05$). While no CLA effect was found in the FO-fed group (FOC), CLA increased the levels of TC in BTC compared to BT at 2 and 4 weeks ($p<0.05$) (Table 5).

There was inconsistency in the levels of HDL-C in our study. While no CLA effect was found in FOC during the experimental period, HDL-C levels were significantly increased in BTC at 2 and 4 weeks ($p<0.05$). Previous studies showed that HDL-C was decreased by CLA.[29] However, other studies reported that HDL-C was not significantly altered by CLA.[30]

The TC/HDL-C ratios showed no significant difference among the experimental groups and experimental periods, even though many reports demonstrated that CLA had beneficial effects on TC and HDL-C.[13,24,31] Lee *et al.*[17] and Jung *et al.*[18] also showed that CLA decreased plasma levels of TC, LDL-C and TG. However, in the present study, the TC level was increased significantly in BTC than that in BT, but Lee *et al.*[17] used high chol diet in rabbits and Jung *et al.*[18] used a similar diet to our study in rats, respectively. Although direct comparisons are not possible with our study, different diet compositions and species may account for the inconsistent results. There are also possibilities that CLA influences differently according to the types of fats used in the diets and that CLA addition may cause fatty acid compositions more profoundly than what we know.

Taken these results together, CLA has more synergistic actions in reducing body fat when supplemented in the diets containing BT rather than FO. Furthermore, it is interesting to see that CLA increased TC level, in particular, in the BT-fed (BTC) group. We should learn more about the effects of CLA and its actions at various levels of physiology and molecular biology. Also some approaches have been already adopted in the right directions.[32]

3. Correlation of the Parameters

When we consideredthe correlations between the body fat accumulations and the related factors at 4 weeks when CLA was most effective in this study, the increase in the body weight showed a positive correlation with the triglyceride concentration (Table 6). The increase in the body weight led to the increase in the triglyceride concentration in the plasma. It was also found that the

Table 6. Correlation coefficient between parameters of mice fed experimental diets for 4 weeks

	Cholesterol	HDL-Chol	FFA	Weight gain	Epidydimal fat	Visceral fat
Triglyceride	0.0847	0.1174	0.8195***	0.3983*	0.7278***	0.6808**
Cholesterol	-	0.9192***	-0.0007	-0.1066	-0.4075*	-0.2540
HDL-Chol	-	-	-0.0297	-0.0371	-0.2857	-0.2071
FFA	-	-	-	0.3624*	0.6315***	0.5458**
Weight gain	-	-	-	-	0.3257	0.1935
Epididymal fat	-	-	-	-	-	0.8349***

* $P<0.05$, ** $P<0.01$, *** $P<0.001$
HDL-Chol: High density lipoprotein cholesterol
FFA: Free fatty acid

epididymal and visceral fats depot showed positive correlations with the levels of triglyceride and free fatty acids. Therefore, as body fat increases, more fatty acids enter the blood stream, leading to higher levels of triglycerides in the plasma.

In conclusion, 0.5% CLA supplement did not show any change in the body weight regardless of fat sources and feeding periods up to 4 weeks in mice. However, CLA with BT rather than FO affects beneficially the levels of epididymal and visceral fat depots, triglycerides, HDL-C and free fatty acids in plasma at 4 weeks rather than 1 and 2 weeks. Further study should focus on how CLA alter the fatty acids composition in the body.

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