

Effect of conjugated linoleic acid on body composition and plasma lipids in humans: an overview of the literature^{1,2}

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ABSTRACT

Studies in mice have indicated that feeding diets containing 0.5–1% conjugated linoleic acid (CLA) considerably reduces body fat. These findings have attracted much interest because of the potential use of CLA as a tool to promote weight loss in humans. Several CLA studies in humans have now been published, and the objective of the present review was to give an overview of these experiments. Most of the studies were done in free-living subjects and were not strictly controlled for nutrient and energy intakes. None of the studies found a significant reduction in body weight, and only 2 studies showed a significant but relatively small body fat–lowering effect. Some studies suggested that CLA may have a tendency to increase lean body mass. Furthermore, there are indications from animal studies that CLA may have effects on plasma lipids. However, only one study in humans showed a significant HDL-cholesterol-lowering effect of CLA; in all the other studies, there were no significant effects on plasma total, LDL-, and HDL-cholesterol concentrations or on plasma triacylglycerol concentrations. Thus, the results of the studies in humans indicate that the effect of CLA on body fat is considerably less than that anticipated from mice studies and that CLA has no major effect on plasma lipids. *Am J Clin Nutr* 2004;79:352–61.

KEY WORDS Conjugated linoleic acid, body composition, plasma lipids, body fat

INTRODUCTION

Conjugated linoleic acids (CLAs) are a group of isomers of conjugated octadecadienoic acid that occur naturally in food, mostly in dairy products. Ritzenthaler et al (1) reported that the intake of total CLA as measured with the food duplicate method was 212 mg/d for men and 151 mg/d for women. Furthermore, 60% of the CLA intake was derived from dairy products and 37% from meat products, and the *cis*-9, *trans*-11 CLA isomer, also called ruminic acid, accounted for >90% of the total CLA intake. Commercial CLA preparations are produced by isomerization of linoleic acid and contain predominantly *cis*-9, *trans*-11 and *trans*-10, *cis*-12 octadecaenoic acids in a 1:1 ratio (2).

CLA has attracted much interest since the discovery that it has anticarcinogenic (3) and body fat–lowering (4) effects. Furthermore, studies in hamsters (5–8), rats (9, 10), and rabbits (11) suggest that CLA may also have lipid- and atherosclerosis-reducing properties. Park et al (4) were the first to report that the

incorporation of 0.5% (wt:wt) CLA in the diets of mice reduces body fat ≈60%. These findings were confirmed in several other studies with mice (12–14), and additional experiments indicated that this body fat–lowering effect is attributable to the *trans*-10, *cis*-12 isomer (6, 15–18). The body fat–lowering property of CLA was also reported in other experimental animals, such as pigs (19), rats (20), hamsters (21), and chickens (22), but the effect in those animals is less striking than that in mice.

The body fat–lowering effect of CLA in experimental animals has led to the idea that CLA could be used as a tool in body weight management in humans. Several studies in humans have been published, but the results appear to be less promising than was expected (23, 24). In the present article, an overview of the results of these studies in humans is given. Furthermore, the effects of CLA on plasma lipids were measured in several of these studies, and an overview of these results is also presented.

However, CLA, and in particular the *trans*-10, *cis*-12 isomer, also appears to have some less desirable side effects. Mice that were fed the *trans*-10, *cis*-12 CLA isomer had severe hyperinsulinemia and insulin resistance (16, 25, 26), and a similar trend was observed in CLA-fed hamsters (27) and pigs (28). Furthermore, the body fat–lowering effect of the *trans*-10, *cis*-12 isomer in mice was associated with a significant reduction in plasma leptin concentrations (16, 26), and a similar tendency was seen in rats (29, 30). Some studies in mice (25, 31), rats (10), and hamsters (27) also showed a significant increase in plasma glucose concentrations after the animals were fed CLA, and the *trans*-10, *cis*-12 isomer appeared to be responsible for this effect (25, 27). Several studies in humans who consumed CLA have examined these effects, and the results of those studies are also reviewed.

MATERIALS AND METHODS

Only studies that were published as full articles are included in the review. Most of the articles were retrieved from the University of Wisconsin website (32) that keeps track of all the literature

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published on CLA. One study describing the effects of CLA on body composition in humans was not included in this review because of the lack of a control group (33).

The data presented in the tables and the figure were reproduced from the articles or, if possible, calculated from the data given in the original publications. The net effect of CLA on body weight and body fat was also calculated by correcting the changes in the CLA group with those in the control group. The net effect of CLA was calculated as $(V_{f\text{CLA}} - V_{i\text{CLA}}) - (V_{f\text{control}} - V_{i\text{control}})$, where V_i and V_f are the initial and final values, respectively, of the control and CLA groups.

RESULTS

Conjugated linoleic acid preparations and study design

The first studies in humans were done with CLA preparations that contained various CLA isomers (2, 34–36) and were produced by Pharmanutrients Inc (Lake Bluff, IL). Later studies used more-defined CLA preparations that were comprised predominantly of the *trans*-10, *cis*-12 and *cis*-9, *trans*-11 isomers in a 1:1 ratio (Tables 1–3) and were manufactured by Natural Ltd (Hovdebygd, Norway) and Loders Croklaan bv (Wormerveer, Netherlands). Only Riserus et al (45) used a CLA preparation that contained almost exclusively the *trans*-10, *cis*-12 isomer, and Noone et al (43) administered a CLA preparation that contained the *trans*-10, *cis*-12 and *cis*-9, *trans*-11 isomers in a ratio of 2:8. There is substantial evidence that the *trans*-10, *cis*-12 isomer is responsible for the effects of CLA on body fat and lipid metabolism (15, 18), and therefore the dosages of the *trans*-10, *cis*-12 isomer are also given in the tables.

The dosage of total CLA used in the various studies ranged from 1.4 g/d in the study by Mougios et al (40) to 6.8 g/d in the study by Blankson et al (38) (Tables 1–3). These dosages used in humans appear to be comparable with the dosages used in mice studies. The metabolizable energy intake of a reference human weighing 70 kg is ≈ 10 MJ/d, and dosages of 1.4 and 6.8 g total CLA/d translate into intakes of ≈ 0.14 and 0.68 g total CLA/MJ of metabolizable energy, respectively. In most of the mice studies, 0.5–1% total CLA by weight was added to the diets (4, 13, 14). High-fat mice diets have an energy density of ≈ 20 kJ of metabolizable energy/g (14), and the CLA intake was thus ≈ 0.25 –0.5 g total CLA/MJ of metabolizable energy intake.

The CLA preparations in all the studies were administered in the form of capsules, and the number of capsules that had to be taken per day varied from 2 (40) to 12 (38). Compliance with the intake of the capsules ranged from $\approx 77\%$ to 100% (Tables 1–3). In all the studies, one or more groups were administered capsules containing a CLA preparation, and a control group was administered capsules containing a placebo, such as olive oil, sunflower oil, soybean oil, or linoleic or oleic acid (Tables 1–3). In one study (34), CLA was administered in the form of triacylglycerols (TAGs); the other studies did not report whether CLA was administered in the form of TAGs or free fatty acids, but CLA was most likely given as free fatty acids. Most of the experiments were done in free-living subjects and were not strictly controlled for nutrient and energy intake. Only in the studies by Benito et al (34), Medina et al (46), and Zambell et al (36), did the researchers confine the subjects to a metabolic suite and control for food intake.

Most of the studies were designed to examine whether CLA

would promote the loss of body weight and fat. The objective of one study, however, was to learn how CLA would influence the regaining of body weight and fat after a weight-loss program (39). In that study, the subjects were fed a very-low-energy diet (2.1 MJ/d) for 3 wk and lost ≈ 6 kg body wt. Subsequently, the subjects were switched back to their habitual diet, and the effects of CLA on body weight regain and body composition were studied.

Body weight and composition

All the studies indicated that the administration of CLA had no significant effect on body weight or body weight regain (Table 1). After correction for changes in body weight in the control groups, there was a net increase in body weight due to CLA in the body weight regain study by Kamphuis et al (39), and this increase ranged from 0.6 to 2.0 kg. In the other studies, the corrected net change in body weight ranged from an increase of 0.4 kg to a decrease of 2.2 kg. None of these changes, however, were significant (Figure 1).

There was a significant effect of CLA on body fat mass in only 2 studies (38, 42). This effect could not be ascribed to a higher intake of CLA in these studies than in the other studies, and there appeared to be no relation between the dose of *trans*-10, *cis*-12 isomer, the isomer involved in the body fat-lowering effect, and the body fat-lowering effect (Figure 1). Furthermore, in these 2 studies that reported a significant body fat-lowering effect of CLA, the subjects also participated in a light or intensive training program (38) or did 90 min of strenuous exercise 3 times/wk (42). Thus, it is possible that exercise may have enhanced the body fat-lowering effect of CLA.

In the studies by Berven et al (37), Blankson et al (38), and Thom et al (42), the net decrease in body fat tended to be greater than the net decrease in body weight, and in the study by Smedman and Vessby (41), there was a slight net increase in body weight but a net decrease in body fat. This finding indicates that in these studies, a change took place not only in body fat but also in lean body mass (LBM). A net decrease in body fat that was greater than the net decrease in body weight indicates that there was an increase in LBM or that the decrease in LBM was less than that in the control group, as seen in the study by Berven et al (37). Furthermore, in the weight regain study by Kamphuis et al (39), CLA tended to promote body weight regain after a weight-loss regimen, and this net increase in body weight was predominantly due to an increase in LBM (Figure 1).

Plasma lipids

The studies in Table 2 did not show any significant effect of CLA on plasma cholesterol concentrations or on LDL-cholesterol concentrations. In the study by Smedman and Vessby (41), CLA significantly increased total and LDL-cholesterol concentrations, but this increase was not significant in comparison with that seen in the control group. Furthermore, Riserus et al (45) found that, relative to the change in HDL-cholesterol concentrations in the control group, HDL-cholesterol concentrations decreased significantly when the *trans*-10, *cis*-12 isomer was administered but not when a mixture of the *trans*-10, *cis*-12 and *cis*-9, *trans*-11 isomers was administered (44, 45). Mougios et al (40) also reported a significant HDL-cholesterol-lowering effect of CLA, but this change in HDL cholesterol concentration was not significant when compared with that in the control group. Smedman and Vessby (41), on the other hand, found that CLA

TABLE 1
Effect of conjugated linoleic acid (CLA) on body weight and body composition in humans¹

Subjects	Berven et al (37) ²	Blankson et al (38) ³	Kamphuis et al (39) ⁴	Kreider et al (35) ³	Mougiou et al (40) ⁵	Smedman and Vessby (41) ²	Thom et al (42) ⁶	Zambell et al (36) ³
<i>n</i>								
Control group	22	8	13	11	11	24	10	7
CLA group	25	7	14	12	11	26	10	10
Sex	M and F	M and F	M and F	Not given	M and F	M and F	M and F	F
Duration of CLA intake (wk)	12	12	13	4	8	12	12	9
Treatment								
CLA								
Manufacturer	Natural	Natural	Natural	Pharmanutrients	Natural	Natural	Natural	Pharmanutrients
Total dose (g/d)	3.40	3.40	1.8	6.00	0.70/1.40 ⁷	4.20	1.8	3.00
<i>t</i> -10, <i>c</i> -12 isomer (g/d)	1.70	1.70	0.9	1.36	0.35/0.70	2.00	0.9	0.68
<i>c</i> -9, <i>t</i> -11 isomer (g/d)	1.70	1.70	0.9	1.06	0.35/0.70	2.00	0.9	0.53
Placebo	Olive oil	Olive oil	Oleic acid	Olive oil	Soybean oil	Olive oil	Hydrogel	Sunflower oil
Compliance (%)	92	> 77	Not reported	100	100	> 80	> 80	100
BMI								
Control group								
Initial (kg/m ²)	30.1 ± 2.2 ⁸	28.1 ± 2.4	26.1 ± 1.4	25.2 ⁹	22.7 ± 3.3	24.5 ± 4.3	23.3 ± 2.5	22.2 ± 3.4
Final (kg/m ²)	30.0 ± 2.2	28.6 ± 2.6	26.7 ± 1.6	—	22.5 ± 3.4	24.56	—	—
Change (%)	-0.3	1.8	2.3	—	-0.9	-0.2	—	—
CLA group								
Initial (kg/m ²)	29.4 ± 2.6	27.2 ± 1.6	25.6 ± 1.1	—	23.8 ± 2.7	25.5 ± 3.9	23.2 ± 2.4	23.2 ± 1.6
Final (kg/m ²)	29.1 ± 2.6 ¹⁰	27.1 ± 1.9	26.8 ± 1.2	—	23.4 ± 2.5	25.64	—	—
Change (%)	-1.0	-0.4	4.7	—	-1.7	0.5	—	—
Body weight								
Control group								
Initial (kg)	92.1 ± 9.5	80.8 ± 6.4	78.0 ± 8.1	79.5 ± 10.3	68.3 ± 15.0	73.8 ± 15.5	72.0 ± 7.9	63.8 ± 11.6
Final (kg)	91.7 ± 9.2	82.2 ± 7.3	79.4 ± 8.5	79.4 ± 10.9	67.9 ± 15.3	74.0	72.2 ± 7.6	64.28
Change (%)	-0.4	1.7	1.8	-0.1	-0.6	0.3	0.3	0.7
CLA group								
Initial (kg)	89.5 ± 12.4	82.6 ± 8.3	77.6 ± 6.4	82.0 ± 10.7	73.1 ± 7.9	77.1 ± 15.1	71.8 ± 8.3	63.1 ± 6.6
Final (kg)	88.4 ± 12.0 ¹⁰	82.2 ± 9.5	81.0 ± 8.1	82.3 ± 10.7	72.1 ± 7.5	77.5	69.9 ± 8.0	62.86
Change (%)	-1.2	-0.5	4.4	0.4	-1.4	0.5	-2.6	-0.4
Body fat (kg)								
Control group								
Initial (kg)	30.2 ± 7.1	30.8 ± 6.0	24.2 ± 5.5	11.9 ± 5.3	10.6 ± 3.6	21.8	15.8	19.7
Final (kg)	30.5 ± 8.1	32.3 ± 7.4	24.2 ± 5.4	12.0 ± 5.3	10.5 ± 4.1	21.5	16.1	20.0
Change (%)	1.0	5	0	0.8	-0.9	-1.4	1.9	0.2

(Continued)

TABLE 1 (Continued)

	Berven et al (37) ²	Blankson et al (38) ³	Kamphuis et al (39) ⁴	Kreider et al (35) ³	Mougiros et al (40) ⁵	Smedman and Vessby (41) ²	Thom et al (42) ⁶	Zambell et al (36) ³
CLA group								
Initial (kg)	29.4 ± 8.0	30.1 ± 4.8	34.7 ± 9.7	23.8 ± 5.3	23.1 ± 6.4	11.5 ± 6.9	12.0 ± 3.7	22.6
Final (kg)	28.6 ± 8.0	28.3 ± 5.1 ¹⁰	33.4 ± 8.9 ¹⁰	24.0 ± 4.5	22.4 ± 6.0	12.0 ± 6.9	11.5 ± 3.3	21.8
Change (%)	-2.7	-6 ¹¹	-3.7 ¹¹	0.8	-3.0	4.3	-4.2	-3.5 ¹¹
Lean body mass								
Control group								
Initial (kg)	61.9 ± 11.7	45.7 ± 8.9	—	53.9 ± 10.0	52.6 ± 9.1	67.6	57.7	52.0
Final (kg)	60.4 ± 12.5	45.6 ± 9.8	—	55.3 ± 10.0	54.4 ± 9.3	67.4	57.4	52.5
Change (%)	-2.4	-0.2	—	1.1	3.4	-0.3	-0.5	1.0
CLA group								
Initial (kg)	60.1 ± 12.8	47.8 ± 9.3	50.1 ± 11.1	53.8 ± 8.1	57.4 ± 8.7	70.5	61.1	54.5
Final (kg)	59.9 ± 13.1	49.1 ± 9.8	51.0 ± 10.6 ¹⁰	57.1 ± 7.7	60.1 ± 9.3	70.3	60.6	55.7
Change (%)	-0.5	1.7	2.6	6.1	4.7	-0.3	-0.8	2.2

¹ Natural, Natural Ltd (Hovdebyda, Norway); Pharnutrients, Pharnutrients Inc (Lake Bluff, IL).

² Body fat was estimated with a formula containing body weight, height, and bioelectrical impedance as variables. Note that for an unknown reason, the lean body mass and the fat mass did not always add up to the total body weight.

³ Body fat was measured by dual-energy X-ray absorptiometry. Note that the lean body mass and the fat mass did not always add up to the total body weight.

⁴ The objective of the study was to examine the effect of CLA on weight gain after weight loss. The subjects were first fed a very-low-energy diet (2.1MJ/d) for 3 wk and lost ≈5–6 kg body wt. Then the CLA studies were started. Body fat was estimated with the formula of Siri after determination of total body water with the deuterium dilution method.

⁵ Body fat was estimated from skinfold thickness.

⁶ Body fat was estimated with a near-infrared technique.

⁷ Amount during the first 4 wk of the study/amount during the last 4 wk of the study.

⁸ $\bar{x} \pm SD$.

⁹ Mean BMI at the beginning of the experiment of all the 23 subjects who participated in the study.

¹⁰ Significantly different from initial, $P < 0.05$.

¹¹ Significantly different from the control group, $P < 0.05$.

TABLE 2
Effect of conjugated linoleic acid (CLA) on plasma lipid concentrations in humans¹

	Benito et al (34)	Berven et al (37)	Mougios et al (40)	Noone et al (43)		Riserus et al (44)	Riserus et al (45)		Smedman and Vessby (41)
Subjects									
BMI (kg/m ²)	23	30	23	24	24	32	30	31	25
<i>n</i>									
Control group	7	22	11	18	—	10	19	—	24
CLA group	10	25	11	16	17	14	19	19	26
Sex	F	M and F	M and F	M and F	—	M	M	—	M and F
Duration of CLA intake (wk)	9	12	8	8	8	4	4	4	12
Treatment									
CLA									
Manufacturer	Pharmanutrients	Natural	Natural	Loders Croklaan	—	Natural	Natural	—	Natural
Total CLA	3.90	3.40	0.70/1.40 ²	2.02	1.74	4.20	3.40	3.40	4.20
<i>t</i> -10, <i>c</i> -12 isomer	0.88	1.70	0.35/0.70	0.95	0.33	1.94	1.62	3.40	2.00
<i>c</i> -9, <i>t</i> -11 isomer	0.70	1.70	0.35/0.70	0.93	1.35	1.94	1.62	—	2.00
Placebo	Sunflower oil	Olive oil	Soybean oil	Linoleic acid	—	Olive oil	Not given	—	Olive oil
Compliance (%)	100	92	100	96	—	96	90	—	> 80
Cholesterol									
Control group									
Initial (mmol/L)	5.00 ± 0.98 ³	6.00 ± 1.10	4.38 ± 0.61	5.18 ± 1.17	—	6.31 ± 1.01	5.80 ± 1.20	—	5.90 ± 1.10
Final (mmol/L)	4.55 ± 0.86	6.10 ± 1.00	4.58 ± 0.74	5.28 ± 1.02	—	6.31 ± 1.01	5.79	—	6.07
Change (%)	-9.0	1.7	4.6	1.9	—	0	-0.1	—	2.9
CLA group									
Initial (mmol/L)	4.94 ± 0.99	6.40 ± 1.20	4.49 ± 0.98	4.93 ± 1.31	5.01 ± 0.49	6.27 ± 1.25	5.50 ± 0.80	6.00 ± 1.30	5.40 ± 1.00
Final (mmol/L)	4.64 ± 0.71	6.40 ± 1.10	4.32 ± 0.87	4.84 ± 0.95	4.92 ± 0.70	6.35 ± 1.02	5.47	5.99	5.69 ⁴
Change (%)	-6.1	0.0	-3.8	-1.8	-1.8	1.3	-0.5	-0.2	5.3
LDL cholesterol									
Control group									
Initial (mmol/L)	2.82 ± 0.94	4.10 ± 1.10	—	1.77 ± 1.04	—	3.93 ± 0.97	4.00 ± 0.90	—	4.00 ± 1.10
Final (mmol/L)	2.56 ± 0.96	3.80 ± 1.30	—	1.71 ± 0.71	—	3.91 ± 0.91	4.95	—	4.09
Change (%)	-9.1	-7.3	—	-3.4	—	-0.5	-1.3	—	2.3
CLA group									
Initial (mmol/L)	2.83 ± 1.11	4.40 ± 1.10	—	1.65 ± 0.83	1.69 ± 0.70	3.76 ± 0.96	3.80 ± 0.70	4.00 ± 1.10	3.60 ± 1.10
Final (mmol/L)	2.81 ± 0.62	4.40 ± 1.00	—	1.53 ± 0.64	1.54 ± 0.59	3.93 ± 0.90	3.72	3.97	3.80 ⁴
Change (%)	-0.7	0	—	-7.2	-8.8	4.5	-2.1	-0.8	5.6
HDL cholesterol									
Control group									
Initial (mmol/L)	1.50 ± 0.34	1.20 ± 0.20	1.28 ± 0.29	1.27 ± 0.31	—	1.13 ± 0.18	1.00 ± 0.10	—	1.30 ± 0.30
Final (mmol/L)	1.44 ± 0.31	1.20 ± 0.20	1.26 ± 0.30	1.42 ± 0.36	—	1.26 ± 0.11	1.07	—	1.46 ⁴
Change (%)	-4.1	0	-1.6	11.8	—	11.5	6.5	—	12.3
CLA group									
Initial (mmol/L)	1.34 ± 0.20	1.30 ± 0.30	1.42 ± 0.29	1.59 ± 0.57	1.44 ± 0.44	1.12 ± 1.17	1.00 ± 0.20	1.00 ± 0.10	1.20 ± 0.30
Final (mmol/L)	1.34 ± 0.15	1.30 ± 0.20	1.25 ± 0.32 ⁴	1.54 ± 0.42	1.47 ± 0.37	1.18 ± 0.18	0.98	0.96	1.29 ⁴
Change (%)	0	0	-12.0	-3.1	2.1	5.4	-2.0 ⁵	-4.0 ⁵	7.5
TAG									
Control group									
Initial (mmol/L)	0.77 ± 0.21	1.70 ± 0.80	0.97 ± 0.54	1.03 ± 0.43	—	2.81 ± 1.20	2.00 ± 1.00	—	1.30 ± 0.60
Final (mmol/L)	0.58 ± 0.13	1.80 ± 0.80	0.90 ± 0.36	0.94 ± 0.33	—	2.99 ± 1.36	1.80	—	1.07 ⁴
Change (%)	-25.5	5.9	-7.2	-8.7	—	6.4	-10.0	—	-17.6
CLA group									
Initial (mmol/L)	0.85 ± 0.25	1.37 ± 0.50	0.95 ± 0.40	1.20 ± 0.39	1.08 ± 0.32	2.78 ± 1.49	1.70 ± 0.50	2.40 ± 2.20	1.40 ± 0.80
Final (mmol/L)	0.59 ± 0.20 ⁴	1.58 ± 0.70	0.82 ± 0.37	0.95 ± 0.31 ⁴	1.00 ± 0.40	3.00 ± 1.31	1.57	2.42	1.33
Change (%)	-30.0	15.3	-13.7	-20.8	-7.4	7.9	-7.6	0.8	-5.0

¹ Pharmanutrients, Pharmanutrients Inc (Lake Bluff, IL); Natural, Natural Ltd (Hovdebygd, Norway); Lodders Croklaan, Lodders Croklaan bv (Wormerveer, Netherlands); TAG, triacylglycerols.

² Amount during the first 4 wk of the study/amount during the last 4 wk of the study.

³ $\bar{x} \pm$ SD.

⁴ Significantly different from initial, $P < 0.05$.

⁵ Significantly different from the control group, $P < 0.05$.



TABLE 3

Effect of conjugated linoleic acid (CLA) on plasma glucose, insulin, and leptin concentrations in humans¹

	Medina et al (46) ²	Noone et al (43)	Riserus et al (44)	Riserus et al (45)	Smedman and Vessby (41)		
Subjects							
BMI (kg/m ²)							
<i>n</i>	22	24	—	32	30	31	25
Control group	7	18	—	10	19	—	24
CLA group	10	16	17	14	19	19	26
Sex	F	M and F	—	M	M	—	M and F
Duration of CLA intake (wk)	9	8	8	4	12	12	12
Treatment							
CLA							
Manufacturer	Pharmanutrients	Loders Croklaan	—	Natural	Natural	—	Natural
Total CLA	3.00	2.02	1.74	4.20	3.40	3.40	4.20
<i>t</i> -10, <i>c</i> -12 isomer	0.68	0.95	0.33	1.94	1.62	3.40	2.00
<i>c</i> -9, <i>t</i> -11 isomer	0.53	0.93	1.35	1.94	1.62	—	2.00
Placebo	Sunflower oil	Linoleic acid	—	Olive oil	Not given	—	Olive oil
Compliance (%)	100	98	—	96	90	—	> 80
Insulin							
Control group							
Initial (pmol/L)	64.6 ± 34.9 ³	63.6 ± 27.3	—	86.7 ± 40.5	73.2 ± 30.0	—	59.6 ± 104.0
Final (pmol/L)	70.1 ± 34.9	66.5 ± 34.6	—	101.0 ± 51.8	78.72	—	43.1
Change (%)	8.5	4.6	—	16.4	7.5	—	-27.8
CLA group							
Initial (pmol/L)	54.9 ± 32.9	77.2 ± 36.4	65.6 ± 40.2	76.1 ± 40.3	64.8 ± 23.4	68.4 ± 26.4	60.3 ± 57.4
Final (pmol/L)	65.3 ± 19.9	65.2 ± 48.9	65.8 ± 40.0	81.2 ± 36.8	69.6	82.8 ⁴	68.6
Change (%)	18.9	-15.5	0.3	6.7	7.4	21.1	13.7
Glucose							
Control group							
Initial (mmol/L)	4.11 ± 0.45	4.97 ± 0.37	—	5.28 ± 0.73	5.70 ± 0.60	—	4.70 ± 0.50
Final (mmol/L)	4.08 ± 0.58	5.21 ± 0.51	—	5.74 ± 0.85 ⁴	5.56	—	4.64
Change (%)	-0.7	4.8	—	8.7	-2.5	—	-1.3
CLA group							
Initial (mmol/L)	4.04 ± 0.28	4.94 ± 0.31	4.97 ± 0.49	5.44 ± 0.83	5.90 ± 0.70	5.60 ± 0.60	4.40 ± 0.80
Final (mmol/L)	4.10 ± 0.73	4.85 ± 0.40	4.88 ± 0.41	5.69 ± 0.73 ⁴	5.91	5.81 ⁴	4.51
Change (%)	1.5	-1.8	-1.8	4.6	0.2	3.8	2.5
Leptin							
Control group							
Initial (ng/mL)	16.7 ± 11.7	—	—	—	10.4 ± 4.6	—	—
Final (ng/mL)	15.7 ± 12.2	—	—	—	10.9	—	—
Change (%)	-6.0	—	—	—	4.8	—	—
CLA group							
Initial (ng/mL)	16.0 ± 7.9	—	—	—	13.2 ± 10.2	11.6 ± 5.6	—
Final (ng/mL)	15.1 ± 11.4	—	—	—	12.1	11.53	—
Change (%)	-5.6	—	—	—	-8.3	-0.6	—

¹ Pharmanutrients, Pharmanutrients Inc (Lake Bluff, IL); Loder Croklaan, Loders Croklaan bv (Wormerveer, Netherlands); Natural, Natural Ltd (Hovdebygd, Norway). There were no significant differences in changes between the control and CLA groups.

² In this study there was a transient leptin-lowering effect of CLA. Plasma leptin was significantly lower in the CLA group than in the control group after 7 wk, but this difference disappeared after 9 wk.

³ $\bar{x} \pm SD$.

⁴ Significantly different from initial, $P < 0.05$.

significantly increased HDL-cholesterol concentrations, but this increase was smaller than that in the control group; as a consequence, the net effect of CLA on HDL was negative. Plasma TAG concentrations decreased significantly after CLA administration in 2 studies (34, 43), but this decrease was not significant when compared with the change in the control group. Furthermore, this effect on plasma TAG concentrations was seen only when a mixture of the 2 isomers was fed, but not when the *cis*-9, *trans*-11 isomer was given (43).

Plasma insulin, leptin, and glucose

Studies in humans who consumed daily a mixture of the 2 CLA isomers containing 0.7–2.0 g of the *trans*-10, *cis*-12 isomer did not show significant changes in plasma insulin concentrations, although a dose of 2 g of the *trans*-10, *cis*-12 isomer (41) tended to increase insulin concentrations, whereas insulin concentrations in the control group decreased (Table 3). Riserus et al (45), however, reported that humans who consumed as much as 3.4 g



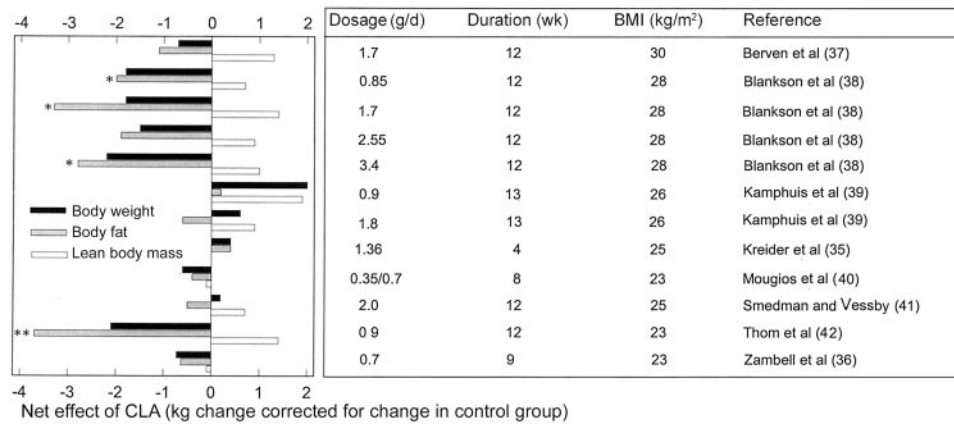


FIGURE 1. Net effect of conjugated linoleic acid (CLA) on body weight, body fat, and lean body mass as observed in various human studies. The net effect was calculated as described in the Materials and Methods section. The BMI values listed are those at the beginning of the study. The dosage values are for the *trans*-10, *cis*-12 CLA isomer, which is the isomer active in lipid metabolism. In the study by Mougios et al (40), 0.35 g of the *trans*-10, *cis*-12 CLA isomer was administered during the first 4 wk of the study, and 0.70 g of the isomer was administered during the last 4 wk of the study. * $P < 0.05$, ** $P < 0.01$.

of the purified *trans*-10, *cis*-12 isomer/d had significantly decreased insulin sensitivity compared with the change in the control group; plasma insulin and glucose concentrations also increased significantly in the CLA group, but these effects were not significant when compared with the changes in the control group.

Leptin is secreted by adipocytes in proportion to the amount of lipid stored and may act as a signal of body energy stores to the brain (47). In humans the consumption of CLA for 9 (46) and 12 wk (45) did not significantly affect leptin concentrations (Table 3). In the study by Medina et al (46), relative to the change in leptin concentrations in the control group, leptin concentrations in the CLA group decreased significantly after 7 wk, but this effect disappeared after 9 wk.

In the study by Riserus et al (44), plasma glucose concentrations increased significantly in both the control group and the CLA group, but this effect was more pronounced in the control group than in the CLA group (Table 3). In another study, Riserus et al (45) reported that plasma glucose concentrations increased significantly only in the CLA group; however, this increase was not significant when compared with the change in the control group. Furthermore, Smedman and Vessby (41) also found higher plasma glucose concentrations in the CLA group than in the control group ($P = 0.054$).

DISCUSSION

Body composition

The effects of CLA on body weight and body fat in humans were considerably less than those seen in mice although the doses of CLA used in the mouse and human studies were comparable. Dosages of 1.4–6.8 g/d in humans (≈ 0.14 – 0.68 g/MJ of metabolizable energy intake) lowered body fat by only 2–22% (Table 1), whereas mice fed 1% CLA in their diet (≈ 0.5 g CLA/MJ) had a 60% decrease in body fat (14). Mice, however, have a considerably higher metabolic rate than do humans, and, as discussed previously (48), this difference in metabolic rate may at least partly explain the different results in humans and mice.

The results in humans did not point to any relation between the dose of CLA and the effect on body weight and fat (Table 1 and Figure 1). Most of the studies, however, were done in free-living

subjects, and variations in nutrient intake and energy intake and expenditure may have occurred. The effects of CLA on body composition appear to be rather small, and thus possible variations in energy intake and expenditure may easily interfere with the effects of CLA. Furthermore, compliance with the intake of the CLA capsules ranged from $\approx 77\%$ to 100%, and differences in compliance may also have affected the results.

Some of the studies in humans suggested that the body fat-lowering effect of CLA tended to be associated with an increase in LBM (Table 1), as seen also in mice (14). Studies in mice indicated that CLA may enhance energy expenditure (12, 14) and the oxidation of fatty acids (4), and these processes take place predominantly in muscle tissues, ie, the LBM. An increase in LBM may be an adaptive response to increased energy expenditure. Kamphuis et al (39) reported that resting metabolic rates in humans are related to the amount of LBM and that increases in resting metabolic rates due to consumption of CLA are associated with an increase in the amount of LBM.

Plasma lipids

All the studies in humans indicated that, compared with placebo, CLA had no significant effect on plasma cholesterol concentrations. Similarly, most of the numerous studies in experimental animals such as mice, rats, and pigs did not show any effect on plasma cholesterol concentrations. There are, however, some studies in hamsters (5–8) and rats (9, 10) that reported a significant cholesterol-lowering effect. Furthermore, this cholesterol-lowering effect of CLA in hamsters was seen only when the hamsters were fed the *trans*-10, *cis*-12 isomer, but not when they were fed the *cis*-9, *trans*-11 isomer (5, 6). A study in chickens fed CLA also showed a decrease in plasma cholesterol concentrations (49), but 2 other chicken studies found an increase (22, 50). Thus, only some studies in experimental animals found an effect of CLA on plasma cholesterol concentrations, and the results in humans suggest that CLA does not have a major effect on plasma cholesterol concentrations.

Compared with placebo, CLA had no significant effect on plasma TAG concentrations (Table 2). CLA significantly lowered TAG concentrations in the studies by Noone et al (43) and Benito et al (34), but these decreases were not significant when



compared with the changes in the control groups. Several studies indicated that feeding mice the *trans*-10, *cis*-12 isomer but not the *cis*-9, *trans*-11 isomer decreases the activity of hepatic stearoyl Co-A desaturase (51, 52), an enzyme involved in the desaturation of stearic acid and palmitic acid into oleic acid and palmitoleic acid, respectively. Plasma TAGs are predominantly transported in the VLDL and are synthesized in the liver. Oleic acid is the preferred substrate for the synthesis of TAG (53), and mice with a disruption of the gene for the stearoyl-CoA desaturase enzyme have very low plasma TAG concentrations (54). Moreover, studies in hypertriglyceridemic mice and humans suggest that there is a relation between hepatic stearoyl-CoA desaturase activity and plasma TAG concentrations (55). Thus, one may anticipate that a decrease in stearoyl-CoA desaturase activity due to consumption of the *trans*-10, *cis*-12 isomer will also result in a lowering of plasma TAG concentrations. In vitro studies indicated that the *trans*-10, *cis*-12 isomer inhibits the secretion of TAG (56) and apolipoprotein B in HepG2 cells (57). When compared with placebo, CLA did not have a significant effect on plasma TAG concentrations in the human studies (Table 2). Most of the subjects in these studies, however, had relatively low plasma TAG concentrations, but an effect could become apparent in severely hypertriglyceridemic patients. The results of animal studies are also not conclusive. Some studies in hamsters found a significant reduction in plasma TAG concentrations (6, 58), whereas other hamster studies showed a significant increase (5). Furthermore, these increases and decreases in TAG concentrations were attributable to the *trans*-10, *cis*-12 isomer, whereas the *cis*-9, *trans*-11 isomer did not have any effect (5, 6). In pigs, there was also a trend for increased TAG concentrations (59–61), and one study even found a significant increase in plasma TAG concentrations (62). Similarly, a study in chickens showed a significant increase in plasma TAG concentrations (50), but another study in chickens did not (49). Most of the studies in mice did not show any significant effect of CLA on plasma TAG concentrations, but in one study, plasma TAG concentrations decreased significantly in mice that were fed the *cis*-9, *trans*-11 isomer but not in mice that were fed the *trans*-10, *cis*-12 isomer (25).


Plasma insulin concentrations and insulin resistance

Studies in experimental animals (63) and humans (64–66) have shown a relation between the fatty acid composition of structural lipids (ie, phospholipids) in the cell membranes of skeletal muscle and measures of insulin action. For example, in human studies insulin action was positively correlated with the degree of unsaturation and the proportion of long-chain polyunsaturated fatty acids, particularly arachidonic acid, in muscle phospholipids (64, 65). Furthermore, insulin action was also positively correlated with Δ^5 -desaturase activity as reflected in the proportion of arachidonic acid. The *trans*-10, *cis*-12 CLA isomer is known to inhibit the activity of stearoyl-CoA desaturase or Δ^9 -desaturase (51, 52), and there are indications that this CLA isomer may also decrease the activity of Δ^5 - and Δ^6 -desaturases (67). Δ^9 -Desaturase plays a role in the desaturation process of fatty acids derived from palmitic and stearic acids (n–9 series), and the Δ^5 - and Δ^6 -desaturases play a role in the desaturation process of fatty acids derived from linoleic (n–6 series) and linolenic (n–3 series) acids. Studies in pigs (61, 68–71), rats (72, 73), perch (74), and chickens (22, 49) have indeed shown that the ratio of palmitic acid + stearic acid:palmitoleic acid + oleic acid, an index of Δ^9 -desaturase activity, in-

creases in muscle lipids after animals are fed CLA. Moreover, these studies showed that the degree of unsaturation of the fatty acids in muscle lipids decreases after CLA consumption and that the proportion of arachidonic acid also decreases consistently after CLA consumption, which points to a lowering of Δ^5 -desaturase activity. No studies have examined the effect of CLA on muscle fatty acid composition in mice and humans after consumption of the *trans*-10, *cis*-12 CLA isomer, but similar changes may occur. Thus, the reduced insulin action and increased plasma insulin concentrations due to consumption of the *trans*-10, *cis*-12 CLA isomer may at least partly be related to changes in fatty acid composition, ie, a decreased degree of unsaturation of the fatty acids in the lipids, particularly in the phospholipids in muscles.

Insulin resistance has also been reported to be associated with elevated concentrations of TAGs in muscle tissues (75). As discussed by Nadler and Attie (76), obesity and lipodystrophy in mice are associated with a fatty liver and insulin resistance. In both situations, there is no functional adipose tissue, the lipogenic burden shifts from the adipose tissue to the liver, and lipid deposition in non-adipose tissue takes place. Feeding CLA to mice also results in lipodystrophy together with accumulation of TAGs in the liver (16, 26). There are no studies in mice and humans given CLA that have examined the lipid content of muscle tissues, but studies in CLA-fed pigs (69, 77), perch (74), and rats (73) showed a trend toward an increase in intramuscular fat, and pigs that were fed CLA also tended to have increased insulin concentrations (28). Thus, it is possible that impaired insulin action due to consumption of the *trans*-10, *cis*-12 CLA isomer is also related to an accumulation of TAGs in muscle tissues, a major site of insulin action. In obese Zucker rats (78), however, CLA reduces the amount of intramuscular fat, which may explain why CLA improves insulin action in obese and insulin-resistant rats (78–80).

Conclusions

The CLA isomer that is involved in the body fat-lowering effect and that is active in lipid metabolism is the *trans*-10, *cis*-12 isomer, whereas >90% of the total CLA intake from food in humans is accounted for by the *cis*-9, *trans*-11 isomer. The results of studies in humans indicate that the effect of the *trans*-10, *cis*-12 CLA isomer on body fat is considerably less than that anticipated from mice studies and that CLA has no major effect on plasma lipids. Furthermore, mice studies showed that the *trans*-10, *cis*-12 CLA isomer may have some undesirable side effects, such as insulin resistance, increased plasma insulin concentrations, and decreased plasma leptin concentrations, and there are indications that some of these effects may become apparent in humans. Additional studies that are well controlled for nutrient and energy intakes may be needed, and pure CLA isomers should be used to clearly define the short- and long-term effects and side effects of each individual CLA isomer. 

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