Efficacy of conjugated linoleic acid for reducing fat mass: a meta-analysis in humans[1,2]

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ABSTRACT

Background: Conjugated linoleic acid (CLA) has been shown to be an effective supplement for reducing fat mass in animals, whereas results in humans have been inconsistent.

Objective: This is a meta-analysis of human studies in which CLA was provided as a dietary supplement to test its efficacy in reducing fat mass.

Design: We searched the PubMed database (National Library of Medicine, Bethesda, MD) and references from the resulting search to identify studies in which CLA was provided to humans in randomized, double-blinded, placebo-controlled trials and in which body composition was assessed by using a validated technique.

Results: We identified 18 eligible studies. Of these, 3 were single-isomer studies, and results comparing CLA isomers were inconclusive. We compared the length of treatment by using studies in which a mixture of purified isomers were used and those in which purified *trans*-10,*cis*-12 isomers were used. This comparison indicated that the effect of CLA was linear for up to 6 mo and then slowly approached an asymptote at 2 y. An analysis of the dose effect indicated that fat loss compared with placebo was $-0.024\,\mathrm{kg}\cdot\mathrm{g\,CLA}^{-1}\cdot\mathrm{wk}^{-1}$ ($P = 0.03$). After adjustment to the median dose of 3.2 g CLA/d, CLA was effective and produced a reduction in fat mass for the CLA group alone (0.05 ± 0.05 kg/wk; $P < 0.001$) and for the CLA group compared with placebo (0.09 ± 0.08 kg/wk; $P < 0.001$)

Conclusion: Given at a dose of 3.2 g/d, CLA produces a modest loss in body fat in humans. *Am J Clin Nutr* 2007;85:1203–11.

KEY WORDS Body composition, obesity, weight loss, conjugated linoleic acid

INTRODUCTION

Conjugated linoleic acid (CLA) refers to a group of positional and geometric isomers of linoleic acid that are characterized by the presence of conjugated dienes. CLA is a natural, but minor, component of fats from ruminant animals that enters the human diet primarily in meat and dairy products (1). CLA has been shown to have many biological effects, including anticarcinogenisis, antiatherogenesis, immune modulation, and changes in body composition, and is commercially available as an over-the-counter supplement (2). In nature, the most abundant isomer is *cis*-9,*trans*-11 (*c*9,*t*11), wheras in supplement forms CLA is typically sold as an equal mix of the 2 predominant isomers *c*9,*t*11 and *t*10,*c*12.

Among the most controversial and highly studied physiologic effects of CLA is the influence on body composition. Many animal studies have investigated the effect of CLA on body composition, and although results vary by species, most find that CLA reduces body fat. Mice are most responsive, with treated animals having 60% less total body fat than controls (3). CLA treatment reduced individual fat depots compared with controls by as much as 88% and 61% in retroperitoneal and epididymal fat, respectively, in one study (4) and by ≈50% in each of those depots in another study (5). In pigs, CLA has resulted in 6–25% less total body fat (reviewed in 6). In hamsters, CLA has resulted in 9% (7) to 24% (8) less epididymal fat, 44% less subcutaneous fat (8), and 58% less perirenal fat (9). In rats, some studies have shown no effect of CLA on overall body composition (10, 11), whereas others have shown that feeding CLA from selectively hydrogenated soybean oil resulted in 23% lower total body fat (12).

Animal studies in which specific CLA isomers were used have shown that the effects on body composition are isomer specific. The *t*10, *c*12 isomer has been identified as the one responsible for decreasing body fat (7, 13, 14). Mechanisms by which the *t*10, *c*12 isomer affects body fat include reduction of lipid accumulation by adipocytes mediated through effects on lipoprotein lipase and stearoyl-coenzyme A (Co A) desaturase (reviewed in 15).

On the basis of the effect of CLA in animal studies, there was great potential for CLA to have a beneficial effect on body composition in humans. Of the human CLA trials to date, however, results have been mixed. There have been 18 studies looking at the effect of CLA on weight loss to date: 7 reported decreases in body fat (16–22) and 10 reported no statistical effect (23–32). The open-label component of one study had no concurrent placebo group but did report a significant fat loss from baseline (33). Three studies investigated the effect of CLA on weight and fat regain or maintenance after weight loss on an energy-restricted diet and found no effect of CLA on those parameters (34–36). Because these studies have differed with respect to isomer, dose, and study duration, the purpose of the present meta-analysis was

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to investigate the influence of these factors on the efficacy of CLA as a treatment for improving body composition.

MATERIALS AND METHODS

Studies used

Selection criteria for the present meta-analysis included longitudinal randomized, double-blind, placebo-controlled human clinical trials of CLA in normal weight, overweight, and obese individuals of any age in which information on CLA dose and source or isomer composition were provided. The study by Zambell et al (37) was not included because it was not double-blind. We only included studies in which body-composition data were obtained by using validated techniques such as dual-energy X-ray absorptiometry (DXA), hydrodensitometry, skin-fold thickness, bioimpedence analysis (BIA), air-displacement plethysmography, or total body water by ^{18}O isotope dilution. One study that used near infrared interactance was not included (38) because this method has not proven to be a consistently accurate and precise method of measuring body composition (39). On the basis of these criteria, we identified 18 weight-loss studies and 2 weight-regain or -maintenance studies for inclusion.

Weight-loss studies

In the Atkinson et al (26) study, the subjects were selected on the basis of being overweight or obese [body mass index (BMI; in kg/m^2): 27 to 40] and included men and women 20–50 y of age. Eighty subjects were randomly assigned, but 9 dropped out before the 6-mo follow-up visit. Of the 71 subjects included in the analysis, 36 were in the placebo group (18 women, 18 men) and had a mean (±SD) baseline BMI of 32.7 ± 2.3 and mean age of 40.3 ± 8.2 y. Thirty-five subjects (23 women, 12 men) were in the CLA group and had a mean BMI of 33.3 ± 3.2 and mean age of 42.5 ± 6.5 y (personal communication, RL Atkinson). No significant differences in values for age, height, weight, and BMI were observed between the groups at baseline. The subjects were instructed to take one capsule 3 times each day (before breakfast, lunch, and dinner) so that they received 3 g safflower oil or 90% pure CLA (2.7 g active isomers) daily for 26 wk. The CLA provided an equal mixture of the *c*9, *t*11 and *t*10, *c*12 isomers (Natural Nutrition, Hovdebygda, Norway). Body composition was measured by hydrodensitometry.

For the Berven et al (23) study, the subjects were selected on the basis of being overweight or obese (BMI: 27.5 to 39) and included men and women aged ≥18 y. Sixty subjects were randomly assigned, but 5 dropped out and 8 more were excluded due to poor compliance. Of the 47 subjects included in the analysis, 22 were in the placebo group (8 women, 14 men) and had a mean (±SD) BMI of 30.1 ± 2.2 and mean age of 46.5 ± 7.0 y. Twenty-five subjects (9 women, 16 men) were in the CLA group and had a mean BMI of 29.4 ± 2.6 and mean age of 47.6 ± 7.1 y. No significant differences in values for age, height, weight, and BMI were observed between the groups at baseline. The subjects were instructed to take 2 capsules 3 times each day (before breakfast, lunch, and dinner) so that they received either 4.5 g olive oil or 4.5 g olive oil/CLA mix at 75% (3.4 g CLA) daily for 12 wk. No isomer mix data were reported, but the CLA was the Tonalin brand from Natural, which is reported elsewhere to be an equal mixture of the *c*9, *t*11 and *t*10, *c*12 isomers (17). Body composition was measured by single frequency leg-to-leg BIA.

In the Blankson et al (16) study, the subjects were selected on the basis of being overweight and obese (BMI: 25 to 35) men and women aged ≥18 y. The subjects were instructed to take 4 750 mg capsules 3 times each day (before breakfast, lunch, and dinner) for 12 wk so that they received either 9 g olive oil (placebo) or one of 4 doses of CLA (1.7, 3.4, 5.1, or 6.8 g CLA isomers/d) in a total of 9 g oil. No isomer mix data were reported, but the CLA was the Tonalin brand from Natural, which is reported elsewhere to be an equal mixture of the *c*9, *t*11 and *t*10, *c*12 isomers (17). Sixty subjects were randomly assigned, 8 subjects withdrew in the first 6 wk, and 5 additional subjects withdrew between weeks 6 and 12. Of the 47 subjects still included at 12 wk, the mean (±SD) baseline BMI was 28.1 ± 2.4 (n = 8), 29.9 ± 2.5 (n = 11), 27.2 ± 1.6 (n = 7), 29.4 ± 2.6 (n = 11), and 30.4 ± 3.0 (n = 10) for the placebo and CLA groups in increasing dose order, respectively. No significant differences in age, height, weight, and BMI were observed at baseline between the 52 subjects still included at 6 wk. Body composition was measured by DXA.

The study by Mougios et al (18) was a double-blind, placebo-controlled trial; however, there was no express statement regarding randomization between treatment groups. Twenty-four subjects (14 men, 10 women) were selected on the basis of not being obese (BMI < 30) and were in the age range of 19–24 y. The subjects consumed 2 capsules/d for 4 wk and 4 capsules/d for the next 4 wk. Capsules contained either soybean oil (placebo) or a 70% equal mix of *c*9, *t*11 and *t*10, *c*12 isomers of CLA (TrofoCell, Hamburg, Germany) for a total of 0.7 g and 1.4 g of CLA isomers, respectively, for the 2 phases of the study. For the purpose of our analyses, we used the average dose of 1.05 g CLA for 8 wk. Results from the study represent 22 subjects (13 men, 9 women), 10 from the CLA group and 12 from the placebo group. No significant differences in age, BMI, body fat, or fat mass were observed between groups at baseline. The respective mean (±SD) baseline ages and BMIs were 22.0 ± 1.3 y and 22.7 ± 3.3 for the placebo group and 22.4 ± 1.7 y and 23.8 ± 2.7 for the CLA group. Body composition was measured by skin-fold thickness (10 sites).

Fifty-three subjects (27 men, 26 women) between the ages of 23 and 63 y were included in the study by Smedman et al (19). After a 2-wk run-in period during which all subjects were given placebo capsules (olive oil), the subjects were given 4.2 g CLA/d (equal mix of *c*9, *t*11 and *t*10, *c*12 isomers) or placebo for 12 wk. Although the article is not explicit, we made the assumption that 4.2 g is the amount of CLA isomers, not total oil, in the capsules. The capsules were provided by Natural Ltd (Oslo, Norway). No significant differences were observed between the placebo and CLA groups at baseline in mean (±SD) age (47.6 ± 10.2 and 42.8 ± 13.1, respectively), BMI (24.5 ± 4.3 and 25.5 ± 3.9, respectively), or body fat percentage (29.6 ± 6.9% and 29.3 ± 7.1%, respectively). Body composition was measured by skin-fold thickness measurements and multifrequency BIA.

The trial by Kreider et al (27) included 23 experienced resistance-trained men (>1 y training, current training of ≥3 h/wk). At baseline, the subjects had a mean (±SEM) age of 23 ± 0.8 y, weight of 80.6 ± 2 kg, height of 179 ± 1 cm, and percentage body fat of 15.5 ± 1%. The subjects were paired according to total body mass, fat-free mass, years of training, hours per week of resistance training, and training program type or volume. The subjects received daily either 9 g olive oil or 5.8 g CLA (Tonalin, Pharmanutrients) with 3 g additional fatty acids

for 28 d. The CLA contained ≈23% *t*10, *c*12; 24% *c*11, *t*13; 18% *c*9, *t*11; 17% *t*8, *c*10; and other isomers. Subjects were instructed to ingest capsules with 3 meals each day. Body composition was measured by DXA.

Sixty men were selected for the Riserus et al (24) study on the basis of being abdominally obese (waist girth >102 cm), having a BMI 27 to 39, and being in the age range of 35–65 y. After a 4-wk run-in period, the subjects received 3.4 g daily of either 80% CLA (equal mix of *c*9, *t*11 and *t*10, *c*12 isomers; 2.7 g/d), 75% purified *t*10, *c*12 CLA (2.5 g/d), or placebo for 12 wk. The capsules were prepared by Natural Lipids (Hovdebygda, Norway). The content of the placebo capsules was not provided in the article. Fifty-seven subjects were included in the final data analyses. No significant differences in any of the baseline characteristics measured were observed between the groups. For the placebo, CLA, and *t*10, *c*12 groups, the mean (±SD) baseline age was 53 ± 10.1, 51 ± 7.1, 55 ± 7.1 y and the mean (±SD) baseline BMI was 30.2 ± 1.8, 30.1 ± 1.8, and 31.2 ± 2.5, respectively. Body composition was measured by BIA by using a multifrequency analyzer.

The study by Petridou et al (29) was a randomized, double-blind, crossover trial. Seventeen sedentary women were selected on the basis of not being obese (BMI < 30) and were in the age range of 19–24 y. The subjects received six 500-mg capsules/d containing either soybean oil (placebo) or 70% equal mix of *c*9, *t*11 and *t*10, *c*12 isomers of CLA (TrofoCell, Hamburg, Germany) for a total of 2.1 g CLA isomers daily. The subjects received the placebo and CLA for 45 d each with no washout period in between. Sixteen subjects completed the study (9 in the CLA-placebo group, 7 in the placebo-CLA group). The mean (±SD) age of subjects was 22.3 ± 1.8 y. The mean (±SD) baseline BMI was 23.1 ± 2.4 for the CLA-placebo group and 23.7 ± 2.9 for the placebo-CLA group. Body composition was measured by skin fold thickness measurements (10 sites).

The subjects in the Eyjolfson et al (30) study were selected on the basis of being sedentary. Sixteen subjects (12 women, 4 men) were randomly assigned and instructed to take 4 capsules daily (one each with breakfast, lunch, dinner, and a light evening snack) for 8 wk so that they received either 4 g/d safflower oil (placebo) or 75% CLA (3 g active isomers/d; 35.5% *c*9, *t*11 and 36.8% *t*10, *c*12). The mean (±SEM) baseline age, BMI, and percentage body fat were 21.6 ± 0.8 y, 28.4 ± 3.0, and 25.7 ± 3.8%, respectively, for the placebo group (n = 6) and 21.4 ± 0.5 y, 26.9 ± 1.5, 25.6 ± 2.8%, respectively, for the CLA group (n = 10). Body composition was measured by BIA.

Ninety subjects (45 men, 45 women) were selected for the study by Malpuech-Brugere et al (25) on the basis of being overweight (BMI: 25–30) and were in the age range of 35–65 y. During a 6-wk run-in period, the subjects consumed a dairy beverage daily containing 3 g high oleic acid sunflower oil. The subjects were then randomly assigned to 1 of 5 groups: 3 g high oleic acid sunflower oil; 1.5 g purified *c*9, *t*11 CLA (plus 1.5 g high oleic acid sunflower oil); 3 g purified *c*9, *t*11 CLA; 1.5 g purified *t*10, *c*12 CLA (plus 1.5 g high oleic acid sunflower oil); or 3 g purified *t*10, *c*12 CLA consumed daily as triacylglycerols in a dairy beverage for 18 wk. The CLA isomers used were >80% pure (Natural Lipids, Hovdebygda, Norway), so 1.2 g and 2.4 g were used for dose calculations in these analyses. At baseline (end of run-in period), there was no difference in sex ratio, age, weight, BMI, fat and lean body mass, and daily energy intake between the treatment groups. The mean (±SD) baseline BMI for each group was the following: placebo, 27.7 ± 1.6; low *c*9, *t*11, 27.9 ± 1.7; high *c*9, *t*11, 27.7 ± 1.2; low *t*10, *c*12, 28.4 ± 2.1; and high *t*10, *c*12, 27.1 ± 1.3. Body composition was measured by DXA.

Twenty-five men were selected for another study conducted by Riserus et al (28) on the basis of being abdominally obese (waist girth >102 cm), having a BMI between 27 and 35, and being in the age range of 35–65 y. The subjects received 3 g/d of either placebo (olive oil, n = 12) or purified *c*9, *t*11 CLA (n = 13) for 3 mo. The CLA contained 83.3% of the *c*9, *t*11 isomer, providing 2.5 g of that isomer per day. The *t*10, *c*12 isomer was present at 7.3%, or 0.2 g/d. The capsules were prepared by Natural Lipids (Hovdebygda, Norway). No significant differences in any of the baseline characteristics measured were observed between the groups. For the placebo and *c*9, *t*11 CLA groups, the respective mean (±SD) baseline age was 56 ± 6.0 and 54 ± 5.5 y and the respective mean (±SD) baseline BMI were 30.4 ± 2.5 and 30.6 ± 2.0. Body composition was measured by BIA by using a multifrequency analyzer.

The subjects for the Gaullier et al (17) study were selected on the basis of being overweight (BMI: 25–30) men and women 18–65 y of age. The subjects were instructed to take 6 capsules daily so that they received a total of either 4.5 g olive oil (placebo), 4.5 g 80% CLA in the free fatty acid (FFA) form (3.6 g active CLA isomers), or 4.5 g 76% CLA in the triacylglycerol form (3.4 g active CLA isomers) for 12 mo. Herein, this study was used as 2 separate CLA treatment groups for our analyses. The CLA contained approximately equal amounts of the *c*9, *t*11 and *t*10, *c*12 isomers. One-hundred eighty subjects were randomly assigned. Their mean (±SD) BMIs at baseline were 27.7 ± 1.7 (n = 59; 12 men, 47 women), 28.1 ± 1.5 (n = 61; 10 men, 51 women), and 28.3 ± 1.6 (n = 60; 9 men, 51 women), and their mean (±SD) ages were 45 ± 9.5, 44.5 ± 10.7, 48.0 ± 10.7 y for the placebo, FFA, and triacylglycerol groups, respectively. No differences in weight, BMI, age, alcohol use, tobacco use, exercise, or medical history were observed between the groups at baseline. Body composition was measured by DXA.

A further study by Gaullier et al (33) was an extension of the previous study (17). After the 12-mo randomized, double-blind, placebo controlled trial, 134 of the 157 subjects were included in an open-label study for an additional 12 mo. All subjects were supplemented with 4.5 g CLA in the triacylglycerol form (3.4 g active CLA isomers; Natural Lipids). Forty-seven subjects had previously been supplemented with the triacylglycerol form, 46 had been supplemented with the FFA form, and 41 had received the placebo. Because there was no placebo group in the second year, results from the second year were used only in the analysis of treatment length. Body composition was measured by DXA.

Forty men were selected for the study by Taylor et al (31) on the basis of being 35–60 y old, having a BMI > 27, and having no diabetes, hypertension, or cardiovascular disease. The subjects were instructed to take 4.5 g/d of olive oil (placebo) or CLA (35% *c*9, *t*11 and 36% *t*10, *c*12; ie, 3.2 g CLA isomers/d) for 12 wk. The capsules were supplied by Natural Lipids (Hovdebygda, Norway). No significant differences were observed between placebo and CLA groups at baseline. The mean (±SD) baseline age, BMI, and percentage body fat (measured by BIA) were 47 ± 8 y, 33 ± 3, and 29 ± 3%, respectively, for the placebo group (n = 19) and 45 ± 6 y, 33 ± 3, 28 ± 4%, respectively, for the CLA group (n = 21). Body composition was measured by skin fold thickness measurements (7 sites) and tetrapolar BIA.

Eighty-five subjects in the study by Pinkoski et al (22) were randomly assigned to receive 5 g CLA/d in seven 1-g capsules or 7 g sunflower oil/d (placebo). The CLA supplement contained equal amounts of the *c*9, *t*11 (36.1%) and *t*10, *c*12 (36.3%) isomers. Seventy-six subjects completed the study. The mean (±SD) baseline characteristics of the males and females in the placebo and CLA groups were the following: BMI of 25.2, 24.4, 26.8, and 23.8; and age 23.9 ± 4.1, 26.4 ± 9.2, 26.6 ± 5.7, and 23.8 ± 6.2 y, respectively. No differences in any of the dependent variables were observed between the treatment groups at baseline. The subjects participated in a resistance training program concurrently with the 7-wk supplementation period. The study also included a subset of subjects who participated in a crossover study, but these data were not included in the meta-analysis. Body composition was measured by air-displacement plethysmography.

The subjects for another study by Gaullier et al (20) were selected on the basis of being overweight and obese (BMI 28–32) men and women 18–65 y of age. The subjects received either 3.4 g/d of CLA (4.5 g Clarinol brand; Lipid Nutrition, division of Loders Croklaan, The Netherlands; $n = 59$) or placebo (4.5 g olive oil, $n = 59$). The CLA oil was a mixture containing 37.5% *c*9, *t*11 and 38% *t*10, *c*12. The rest of the mixture was made of other fatty acids (containing <2% of unsaturated fatty acids in the *trans*, *trans* conformation, <7% of saturated fatty acids, and <1% in free fatty acids). One-hundred fifteen subjects were randomly assigned; 105 (21 men, 84 women) completed the 6-mo study; 83 completed the study with >70% pill count compliance (data from these subjects were used for the present meta-analysis). The subjects were on an ad libitum diet, and no restrictions in lifestyle or in caloric intake were implemented. However, on request, the study nurse gave the subjects dietary advice and exercise recommendations of a general nature at the beginning of the study. No significant differences were observed between the placebo and CLA groups at baseline in mean (±SD) age (48.7 ± 9.2 and 45.8 ± 10.0 y, respectively), BMI (30.2 ± 1.4 and 30.5 ± 1.4, respectively), or body fat percentage (42.2 ± 5.6% and 42.3 ± 6.1%, respectively). Body composition was measured by DXA.

Forty-eight subjects were selected for the Watras et al (21) on the basis of being overweight (BMI: 25 to 30) but otherwise healthy and were in the age range of 18–44 y. The subjects received four 1-g capsules daily for 180 d that contained either safflower oil (placebo) or 80% equal mix of *c*9, *t*11 and *t*10, *c*12 isomers of CLA for a total of 3.4 g CLA isomers/d. Forty subjects completed the study (18 in the placebo group, 22 in the CLA group). No significant differences were observed between the placebo and CLA groups at baseline in mean (±SD) age (32 ± 7 and 34 ± 8 y, respectively), BMI (28 ± 2.2 and 27.6 ± 1.8, respectively), or body fat percentage (36.0 ± 4.2% and 33.6 ± 7.4%, respectively). Body composition was measured by the 4-compartment model including body density by hydrodensitometry, body mineral by DXA, and body water by ^{18}O isotope dilution.

Sixty-four subjects were selected for the Lambert et al (32) study on the basis of being nonobese (BMI < 30), healthy men and women between the ages of 21 and 45 y who exercised ≥3 times/wk for >6 mo. Sixty-two subjects completed the trial. The subjects received 3.9 g/d of placebo or CLA supplement (2.57 g active CLA isomers/d; equal mix of *c*9, *t*11 and *t*10, *c*12 isomers). The mean (±SD) age of subjects was 32 ± 7 y. The mean BMI for men was 22.5 ± 2.5 and for women was 24.2 ± 2.1. Body composition was measured by DXA.

Weight regain studies

Of the 3 studies published to date investigating the effect of CLA on weight regain or maintenance after weight loss (34–36), only 2 (34, 35) have been published with sufficient body-composition detail to include in the meta-analysis.

Subjects for the Kamphuis et al (34) study were selected on the basis of being overweight (BMI: 25–30) men and women 20–50 y of age. The subjects were prescribed a very-low-calorie diet (2.1 MJ) for 3 wk before supplementation. They were then randomly assigned to receive 1.8 g oleic acid, 1.8 g CLA, 3.6 g oleic acid, or 3.6 g CLA daily for 13 wk (TonalinTM brand, Hovdebygda, Norway; 75% CLA in the triacylglycerol form). Although the publication is not explicit, we made the assumption that 1.8 and 3.6 g are the amounts of CLA isomers, not total oil, in the capsules. The subjects were instructed to ingest capsules before breakfast, lunch, and dinner. For the low-dose CLA, low-dose placebo, high-dose CLA, and high-dose placebo, the mean (±SD) BMIs before the very-low-calorie diet were 27.6 ± 1.1 ($n = 14$), 28.0 ± 1.6 ($n = 13$), 28.3 ± 1.7 ($n = 13$), and 27.6 ± 1.5 ($n = 14$), respectively, and after the very-low-calorie diet at the beginning of the intervention the BMIs were 25.6 ± 1.1, 26.1 ± 1.4, 26.2 ± 1.7, and 25.7 ± 1.4, respectively. No significant differences in age, body weight, BMI, or percentage body fat were observed between the groups at the start of the study. Body composition was measured by hydrodensitometry and deuterium dilution.

The subjects for the Larsen et al (35) study were selected on the basis of being overweight and obese (BMI: 28–35) men and women 18–65 y of age. The subjects were prescribed a low-calorie diet (3.3–4.2 MJ) for 8 wk before supplementation. The subjects that lost ≥8% of their initial body weight were then randomly assigned to receive 4.5 g olive oil or CLA daily for 13 wk (TonalinTM brand; 80% CLA in the triacylglycerol form; 3.4 g CLA isomers). This protocol involved 8 wk on a low-calorie diet before the 52-wk intervention with CLA or placebo. Although body weight, BMI, body fat mass, and fat free mass were significantly higher in the placebo group than in the CLA group at weeks −8 (before the low-calorie diet) and 0 (baseline), the percentage body fat mass was not significantly different between groups at weeks −8 or 0, nor was the change from week −8 to week 0 significantly different for any of these variables. Body composition was measured by DXA.

Statistical analyses

Each treatment group was used as a single data point without weighting. The effect of dose was assessed by using least-squares linear regression analysis. The original authors' 95% CIs were used in the meta-analysis if provided or were calculated from the published SD and the sample size. Several publications did not provide enough data to calculate the 95% CI, as indicated on the appropriate figure. Fat loss data were used as published for the meta-analysis. A second analysis was then performed with adjustment for doses of CLA that differed from 3.2 g/d by using the β coefficient from the linear regression of fat loss on dose. Statistical significance was set at $P \leq 0.05$. Data are presented as means ± SDs unless otherwise indicated.

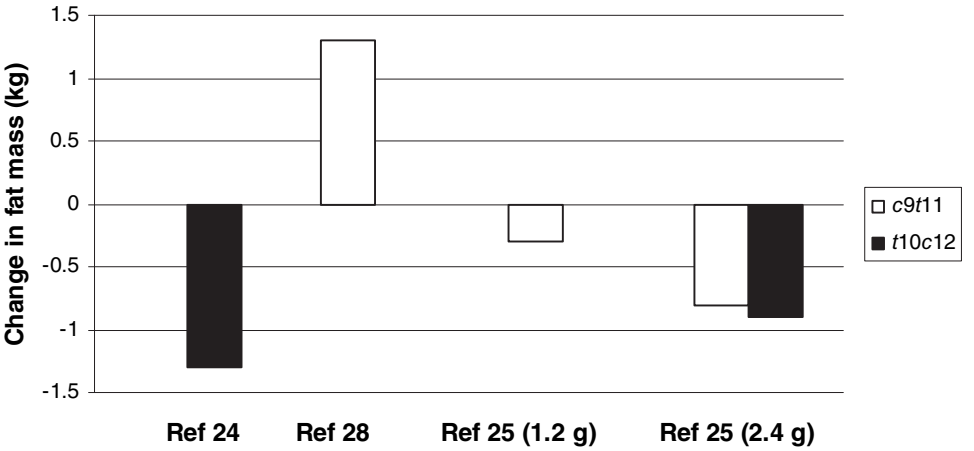

FIGURE 1. Changes in fat mass from single-isomer conjugated linoleic acid studies.

RESULTS

Only 3 studies investigating single isomers conducted in humans were identified (24, 25, 28). The *t*10, *c*12 isomer had no significant effect (**Figure 1**) in one group given a low dose (26), but decreased body fat in the other 2 groups (24, 25). No conclusion can be reached on the specificity of the isomers for fat loss based on these 3 human studies. However, as indicated in the introduction, animal studies have shown that *t*10, *c*12 is the isomer that has the greatest effect on body fat. Therefore, we did not include the treatment groups that only received *c*9, *t*11 CLA isomers in the following analyses (25, 28).

The effect of dose was investigated by plotting the change in fat mass (kg/wk) against the dose of CLA (g/d). The change in fat mass represented the difference between the CLA and placebo groups from baseline (**Figure 2**). One study was found to be an outlier based on the residual being >2 times the SEE and was not included in the regression analysis (27). The results at 2 y from the Gaullier et al (33) study were not included because there was no placebo group for calculating relative change in fat mass during the second year. The regression was significant ($R^2 = 0.1771$, $P = 0.03$), indicating that there was a dose effect with a slope of -0.024 kg fat $\cdot$ g CLA^{-1} $\cdot$ wk^{-1}. When fat loss of the CLA group alone (not relative to placebo) was expressed as kg/wk against the dose of CLA in grams per day (data not shown), the effect was not significant ($R^2 = 0.053$).

The change in fat mass in the CLA treated group was plotted against the length of the study (**Figure 3**). The 2 data points available at the 104-wk time point are from a single study (33) and represent subjects who were taking CLA as either FFA or triacylglycerols for the first 52 wk and CLA as triacylglycerols for the second 52 wk. The change in fat mass expressed as kg/wk (to normalize for the length of the treatment) is shown in **Figure 4** for the CLA group alone and **Figure 5** for the fat loss in the CLA group relative to the placebo control. The average fat loss is 0.05 ± 0.05 kg/wk ($P < 0.001$) for the CLA group alone and 0.09 ± 0.08 kg/wk ($P < 0.001$) for the fat loss compared with the placebo control group. Considering the plateau effect of CLA over time (Figure 3), the data from 104 wk was not included in Figures 4 and 5.

Data shown in Figures 4 and 5 were derived by using CLA at various doses from 1 to 6.8 g/d and thus are influenced by the dose effect shown in Figure 2. When the fat loss (in kg/wk) was adjusted by linear regression to the mean dose of 3.2 g/d, the average fat loss for the CLA group alone (0.05 ± 0.05 kg/wk) and for the CLA group relative to placebo (0.09 ± 0.07 kg/wk) were not significantly different from those calculated for each individual dose.

In addition to the above fat loss CLA trials, 2 studies have been published in which CLA and placebo were provided to test whether CLA could prevent or reduce fat regain after weight loss (34, 35). Analysis of these 2 studies indicated the average fat loss for the CLA group alone was 0.007 kg/wk (95% CI: -0.053, 0.039 kg/wk) and for the CLA group relative to placebo was 0.018 kg/wk (95% CI: -0.076, 0.040 kg/wk). Although the trend for CLA was favorable, it was much smaller than the effect reported above for fat loss and was not statistically significant.

DISCUSSION

Despite the multitude of human clinical trials testing the effect of CLA on body composition, the effect of CLA has been controversial because significant effects of CLA on body fat have not been consistently reported. Our analyses combine the varied study results to draw conclusions about the body of evidence as a whole. In our analyses, we were able to focus the studies to show that CLA does indeed cause a modest, but significant,

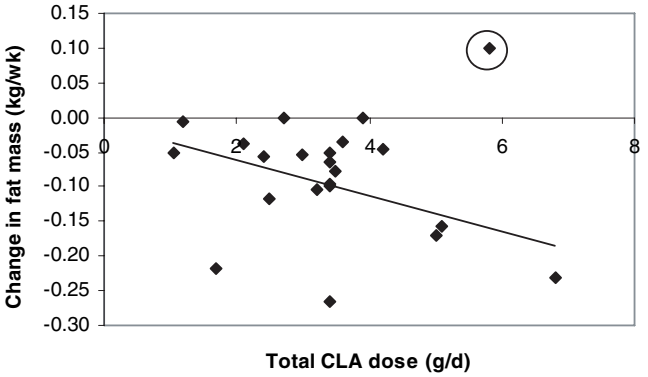

FIGURE 2. The effect of conjugated linoleic acid (CLA) dose on rate of change in fat mass. The rate of change in fat mass due to CLA dose was calculated relative to that obtained with placebo. The encircled data point from the study by Kreider et al (27) qualifies as an outlier and was not included in the regression analysis. The results from the Gaullier et al (33) study were excluded because of a lack of placebo group for 2-y comparison.

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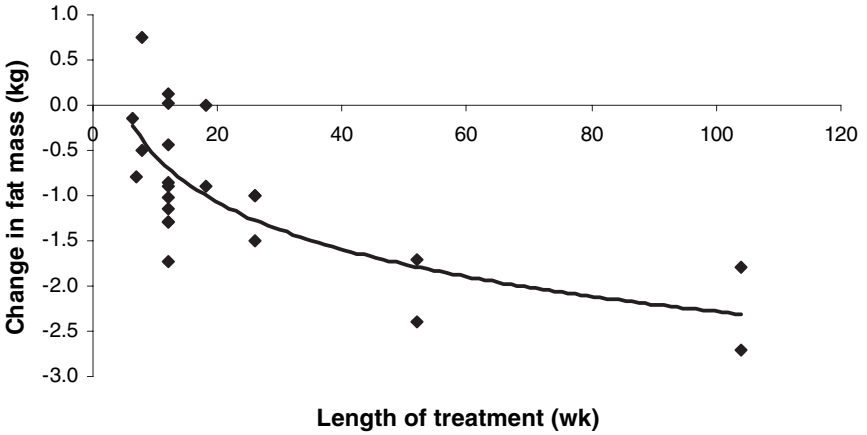

FIGURE 3. Change in fat mass with increasing conjugated linoleic acid treatment length.

reduction in fat loss of about 0.09 kg/wk relative to subjects in placebo groups. Although this effect is seemingly of little consequence, it is larger than and in the opposite direction to the current trend for Americans to gain an average of 0.4 kg total weight each year (0.009 kg/wk) (40).

As shown in Figure 2, an analysis of multiple studies indicates that there is a significant CLA dose effect in humans. In the one human study in which doses were directly compared, however, a dose of 3.4 g/d resulted in a weight loss of 0.14 kg/wk, whereas the 6.8 g/d dose resulted in a weight loss of 0.11 kg/wk (16). The failure to show a dose effect in this single study compared with the cumulative data from multiple studies reflects the inherent variability of fat loss in free-living humans. The highest dose provided in a human trial to date is 6.8 g/d (50:50 mixture of the *t*10, *c*12 and *c*9, *t*11 isomers) (16). There is insufficient human data to determine whether higher doses will produce more weight loss. Based on animal studies, it is possible that doses higher than 6.8 g CLA/d would produce additional fat loss. It is difficult to predict, however, because it is not obvious how to scale the doses between mice and humans. In animal studies that showed larger relative effects on fat mass than those we summarize here for human studies, doses have been provided in the range of 0.1% to 1% of the diet as CLA. Based on dose per body weight, these doses in a mouse provide 0.2 to 3 g/kg and are much larger than the 0.015 to 0.1 g/kg doses used in these human studies. On the basis of percentage energy intake, however, the 0.1% to 1% of diet doses in the mouse corresponds to doses between 0.2% and 2% of energy and would translate to adult human doses between 0.5 and 5 g CLA/d.

Most CLA studies reviewed were ≤12 wk in length. Overall, fat loss was nearly linear for the first 6 mo of treatment and then began decelerate and to approach an asymptote, based largely on the single 2 y study (33). In contrast, most control groups would be predicted to gain a small amount of fat mass during a 2-y interval, so preventing gains in fat mass during long-term CLA treatment has a potential health advantage. Unfortunately, this single 2-y study was performed open label and did not include a placebo group for the second year (33). Therefore, it is not possible to reach definitive conclusions about potential body-composition benefits of CLA consumption for longer periods of time.

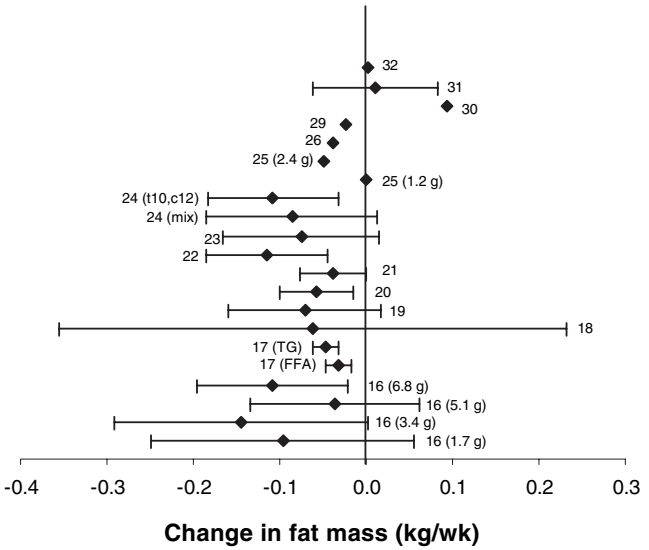

FIGURE 4. Mean (95% CI) rate of change in fat mass with conjugated linoleic acid supplementation. Numbers are reference numbers. Error data were not available where error bars are not shown. TG, triacylglycerols; FFA, free fatty acids.

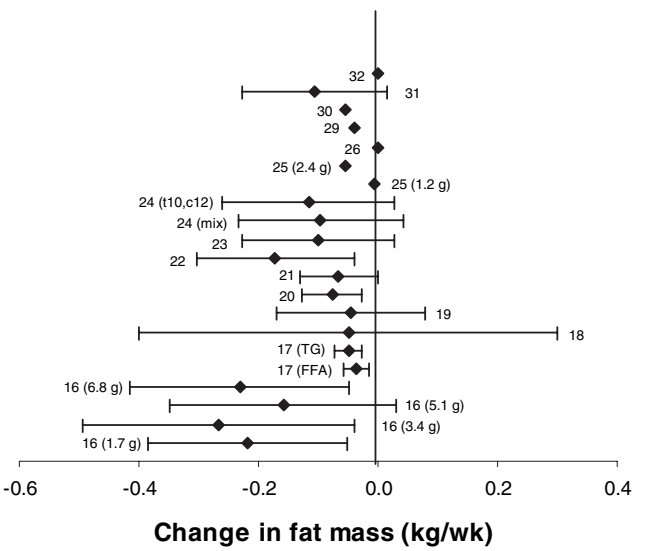

FIGURE 5. Mean (95% CI) rate of change in fat mass with conjugated linoleic acid treatment compared with placebo. Numbers are reference numbers. Error data were not available where error bars are not shown. TG, triacylglycerol; FFA, fatty acids.

Very few data are available on individual CLA isomers and body composition. The results of the 3 single isomer studies, however, are not inconsistent with animal studies showing the *t*10, *c*12 isomer to be the efficacious isomer for body composition (7, 13, 14). For most human studies, the *t*10, *c*12 isomer was provided as an equal mix with the *c*9, *t*11 isomer. There are inadequate data to indicate an ideal mix of isomers for body composition, but the data available to date indicate that a mixture of *t*10, *c*12 and *c*9, *t*11 results in no severe adverse events, although the one human study that used the *t*10, *c*12 isomer alone did result in transient insulin resistance within 12 wk (24).

We separately analyzed 2 studies that were designed to look at the effect of CLA on body composition during the regain phase that is typically experienced after weight loss on an energy-restricted diet. Both studies found no effect of CLA on fat and total weight during weight regain (34, 35), although one study found that CLA significantly increased fat-free mass (34). Based on these limited data, it is not possible to draw any conclusions at this time regarding the effect of CLA on long-term weight maintenance because the 95% CIs are large and include fat loss and gain. Further studies to test the efficacy of CLA during regain are needed.

Our findings indicate that the 10 human studies that showed no statistically significant effect of CLA on fat mass lacked statistical power because the treatment duration was too short, there were too few subjects, or both. For example, based on the average difference in change in fat mass of 0.09 kg/wk between CLA treatment and placebo, the expected difference at 12 wk would be 1.1 kg. Because the average SD for within-individual change in fat mass was 2.6 kg, it is estimated that it would require 44 participants in each group to have an 80% power to detect this change with a $P < 0.05$. Thus, it is not surprising that only a portion of the previous studies found statistically significant differences in fat mass.

Although no severe adverse events have been related to the use of CLA, there are reports of effects of CLA on several risk factors for chronic disease (reviewed in 41 and 42). CLA has been shown to slightly increase biomarkers of inflammatory disease (usually within the published normal values), including C-reactive protein (43), white blood cell counts (33, 35), and blood and urinary isoprostanes (24). Elevations of these biomarkers have been suggested to be indicators of inflammatory disease (44–46) but have also been shown to be antiinflammatory (47). In addition, although CLA does increase these suggested biomarkers of inflammation, animal studies strongly suggest that CLA is not proinflammatory but antiinflammatory. CLA decreased and reversed atherosclerosis (48–50), decreased antigen-induced airway hypersensitivity (51–52) and improved airway response in humans (53), increased life expectancy in a mouse lupus model (54), decreased inflammation in a model of arthritis (55), decreased bowel inflammation in a pig model (56), and reduced endotoxin-induced (57) and cancer-induced (58) cachexia in many animal models. Thus, although CLA has been shown to cause a modest increase in inflammatory markers, it has also been shown to decrease inflammatory disease in several models. The relevance of these elevated biomarkers of inflammation taking into account the decrease in inflammatory disease remains to be determined.

CLA has also been reported to increase insulin resistance (24, 28, 59). This has been most notable in studies of short duration (59), those that used single isomers (24, 28), or both. For example, in one study, insulin resistance was reported in individuals supplemented with only the *t*10, *c*12 isomer for 12 wk, but not with a mixed preparation of predominantly the *c*9, *t*11 and *t*10, *c*12 isomers (24). In a later study, the same enriched *t*10, *c*12 supplement was given for 18 wk and did not result in insulin resistance (25). Many studies either have not found significant changes in fasting glucose or insulin or in measures of insulin sensitivity (17, 19, 25, 27, 31, 32, 34–36, 60–67) or have found an improvement (30, 35, 62). With regard to both safety and efficacy, it has been suggested that CLA preparations enriched in *c*9, *t*11 and *t*10, *c*12 isomers are preferable to preparations containing 4 isomers (41), and this may also be true compared with single isomer preparations. Further investigation into the safety of CLA is warranted.

In conclusion, when the body of evidence is considered as a whole, CLA does have a beneficial effect on human body composition. Although this effect is modest, it could be important if accumulated over time, especially in an environment where continuous, gradual weight gain is the norm in the adult population.

The authors' responsibilities were as follows: ACW performed the initial literature search and acquired publications; DAS performed statistical analysis and wrote the manuscript; and LDW performed statistical analyses and wrote the manuscript. All authors were involved in reviewing the final draft of the manuscript. LDW is coinventor on US Patent no. 6 077 868 (Selective inhibition of cyclooxygenase-2), a CLA-related patent (assignee: Wisconsin Alumni Research Foundation, currently licensed as part of a series of patents by 4 corporations). DAS was a previous recipient of a grant from Cognis Nutrition and Health in support of a human clinical trial of CLA. ACW has no conflict of interest.

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