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Conjugated linoleic acid (CLA) and obesity

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Abstract

Background: The term conjugated linoleic acid (CLA) refers to several positional and geometric conjugated dienoic isomers of linoleic acid (LA), of which the trans-10,cis-12 isomer has been reported to reduce adiposity and increase lean mass in mice and other animals when included at ≤1% of the diet. However, most dietary CLA in humans is obtained from dairy products, accounting for the cis-9,trans-11 CLA isomer, also known as rumenic acid, for more than 90% of the total CLA intake. Commercial CLA preparations industrially produced, containing trans-10,cis-12 and cis-9,trans-11 CLA isomers in diverse proportions, are attracting consumers' interest because of the purported body fat-lowering effects of CLA, coupled to the perception of a 'natural' compound devoid of harmful effects. Nevertheless, despite numerous studies on CLA effects on body composition for nearly a decade, the mechanisms by which CLA isomers elicit their effects remain largely unknown. The purpose of this paper is to provide an updated review of the studies performed on animals and humans, as well as to describe the potential mechanisms involved in CLA effects on body weight and composition and metabolism.
Method: Literature review.
Results: Experiments in humans have not been able to show a significant effect on body weight, body composition or weight regain related to either of the CLA isomers. In fact, some studies suggest a tendency towards a decrease in body fat mass and an increase in body lean mass, while some others raise concern about the possibility of deleterious effects of trans-10,cis-12 CLA on lipid profile, glucose metabolism and insulin sensitivity.
Conclusions: Evidence regarding effectiveness of CLA in humans is not concluding.

Keywords
CLA fatty acid
Obesity
Anti-obesity agents
Body composition
Lipid metabolism
Insulin resistance
Diabetes mellitus type 2

The term conjugated linoleic acid (CLA) refers to several positional and geometric conjugated dienoic isomers of linoleic acid (LA). LA, or cis,cis-9, 12-octadecadienoic acid, is an 18-carbon omega-6 fatty acid (18:2, 9c–12c) abundant in seed oils, such as sunflower oil. LA is converted to CLA when a chemical or microbial reaction shifts the double bonds to form alternating double and single bonds, hence the term *conjugated*. These double bonds can be located in different positions along the 18-carbon chain (7,9; 8,10; 9,11; 10,12; 11,13). This conjugation of the double bonds can alter the geometrical isomery of the acid, so that one or both double bonds can adopt trans isomery. The two isomers with known biological activity are cis-9,trans-11 and trans-10,cis-12 CLA.

CLA potential effects on health include anticarcinogenic, antiatherogenic, antidiabetogenic and immune modulating properties[1,2]. CLA has also attracted interest in the scientific community because of its potential effects on body composition, reducing body fat mass and increasing the lean mass. Because of the increasing prevalence and incidence of obesity, a significant proportion of consumers are interested in CLA supplements with purported body fat-lowering effects, perceived as a 'natural' compound devoid of harmful effects.

Sources of conjugated linoleic acid

Rumiant animals are able to synthesise CLA through the microbial isomerisation (*Butyrinvibrio fibrisolvens* and other anaerobic bacteria) of dietary LA in their gastrointestinal tracts[3]. Rumiant meat (beef, veal, lamb) and dairy products are rich in cis-9,trans-11 CLA, also known as rumenic acid. Rumenic acid is the first intermediate step in the biohydrogenation of LA to stearic acid (C18:0).

CLA isomers can also be industrially produced by heating LA in the presence of alkali or by partial hydrogenation of LA. CLA that is typically produced for experimental purposes (MI-CLA) consists of the cis-9,trans-11 (40.8–41.1%), trans-10,cis-12 (43.5–44.9%)

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Table 1 Effects of CLA isomers on body weight and composition

	Animals (mice and others)	Humans
Trans-10,cis-12 CLA	↓ body fat mass[10–14] ↑ body lean mass[10–14] ↓ body weight[10–14]	No effects on body weight[23–26] No effects on weight regain[27,28] ↓ body fat mass?[30–33] ↑ body lean mass?[27,29,30–33]
Cis-9,trans-11 CLA	↑ feed efficiency and growth in weanling animals[10,14,18–20]	

CLA – conjugated linoleic acid.
↑ – increase; ↓ – decrease; ? – possible.

and trans-9,trans-11/trans-10,trans-12 (4.6–10%) isomers[4]. It should be noted that some commercial CLA preparations contain additional isomers with conjugated double bonds at the 8,10 or 11,13 positions[5].

The major dietary sources of CLA for humans are beef and dairy products. Cis-9,trans-11 CLA is the principal CLA isomer in milkfat[4]. Several factors influence CLA content of food products, such as animal's diet, age, breed or seasonal factors, reaching the highest levels in cow's milk during the spring and summer, as cows are allowed to graze in pastures[6]. CLA in milk or meat is a stable compound under normal cooking and storage conditions[7].

Total CLA content in milk or dairy products ranges from 0.34% to 1.07% of total fat[7], whereas in raw or processed beef it ranges from 0.12% to 0.68% of total fat[7]. CLA daily intakes are 212 mg for men and 151 mg for women not consuming CLA commercial preparations. Most dietary CLA is obtained from dairy products, accounting for the cis-9,trans-11 CLA isomer for more than 90% of the total CLA intake[8].

Evidence of conjugated linoleic acid effects on body weight in animals

Interest in CLA started in 1987, when Ha *et al.*[9] reported that CLA present in fried ground beef, also synthetically produced by base-catalysed isomerisation of LA, was an effective inhibitor of benzopyrene-initiated mouse epidermal neoplasia.

Regarding obesity and body composition, several studies in animals have shown the ability of CLA to reduce adiposity and increase lean mass. Park *et al.*[10] were the first to report that dietary CLA could alter body composition. A diet containing 0.5% MI-CLA administered to the ICR (Institute for Cancer Research) line of mice caused a 60% decrease in body fat, coupled with enhanced lean body mass, after about 4–5 weeks of feeding.

CLA has also been reported to lower fat mass in other lines of mice[4], as well as in Sprague–Dawley[11] and Zucker rats[12], though not reaching such impressive results as in mice. In swine, MI-CLA decreased fat deposition and increased lean tissue too[13,14]. Interestingly, MI-CLA-supplemented diet increased fat deposition in obese Zucker rats[12], while reducing insulin levels.

CLA does not reduce food intake in rodents[15,16] and its effects are independent of fat content of the diet[15]. Conversely, dietary protein source may alter the effects of CLA on adipocytes' fat content and adipocytokine production, as rats fed with soy diet show more pronounced fat loss and different changes in leptin and adiponectin levels compared to their casein-fed counterparts[17].

There is substantial evidence that CLA reduces body fat gain in young growing animals[10,14,18–20] although some study results do not strongly confirm this[21]. CLA supplementation during gestation and lactation elicits greater body weight and feed efficiency in weanling mice relative to control animals[22]. This effect on feed efficiency and growth seems to be exerted by the cis-9,trans-11 isomer[4].

Reported effects of CLA on body weight and composition in animals are summarised in Table 1.

Evidence of conjugated linoleic acid effects on body weight in humans

Experiments in humans have not been able to show a significant effect on body weight related to either MI-, cis-9,trans-11 or trans-10,cis-12 CLA[23–26]. Published studies report contradicting results. Although in the majority of them there are no significant differences on body weight, body composition[26] or weight regain[27,28] between controls and CLA-supplemented groups, some studies suggest that CLA might have a tendency to increase lean body mass[27,29,30]. On one hand, one study carried out in overweight/obese adult volunteers[30] report a reduction in body fat mass with doses $\geq$3.4 g MI-CLA per day at week 12 (150–580 g more than placebo), with a significant increase in body lean mass in the group that received 6.8 g MI-CLA per day, measured by dual-energy X-ray absorptiometry; however, this group was also the only one with a significant increase in exercise level. Similar effects were detected in other human trials with MI- and trans-10,cis-12 CLA[31].

On the other hand, another recent study designed to assess the effect of 1-year supplementation with 3.4 g day^{-1} CLA in body weight or body fat regain found no differences against placebo[28,32]. In a recent meta-analysis at a dose of 3.2 g day^{-1}, CLA was found to produce a slight reduction in fat mass peaking at 6 months, although confidence intervals were broad.

Differences in doses (ranging from 0.7 to 6.8 g day^{-1})[30–33], treatment compliance, type and/or proportion

of the administered isomer/s, length of the study, characteristics of the study population, energy expenditure and nutrient and energy intakes are possible explanations for the observed discrepancies in the results. Noteworthy, there is no clear dose–response related to the body fat-lowering effect of trans-10,cis-12 CLA and in most of the studies that reported a significant decrease of body fat mass or in those suggesting an increase in lean mass, the participants were also involved in a training programme or did a considerable amount of exercise[30,33]. Therefore, exercise might enhance the body fat lowering and/or lean mass increasing effect of CLA.

The effects of CLA on body weight and composition in humans are summarised in Table 1.

Effects of conjugated linoleic acid on adipocytes

Although the mechanisms by which CLA exerts its action on body weight have not been fully elucidated yet, it seems clear that trans-10,cis-12 CLA is the isomer involved in the changes of body composition.

Trans-10,cis-12 CLA and/or its metabolites is/are able to reduce lipid uptake by adipocytes due to the inhibitory effects on gene expression and enzymatic activity of stearoyl-CoA desaturase (SCD)[34,35] and lipoprotein lipase (LPL)[10,36,37]. Trans-10,cis-12 CLA also inhibits the expression of glucose transporter-4 (GLUT-4)[37,38] and increases the activity of carnitine palmitoyltransferase (CPT), enhancing fatty acid oxidation[10]. Trans-10,cis-12 CLA reduces lipogenesis in human[37] and mice adipocytes, decreasing sterol regulatory element-binding protein-1 (SREBP-1) expression *in vivo*[39]. Trans-10,cis-12 CLA also induces adipocyte apoptosis in mice[39–43], perhaps mediated by an increase in tumour necrosis factor alpha (TNFα)[39], but the effects of CLA on lipolysis *in vivo* and *in vitro* are conflicting[10,38]. Data regarding its effects on preadipocyte differentiation are inconclusive, possibly depending on species, CLA isomer and experimental conditions[4,37]. Chronic treatment with trans-10,cis-12 CLA significantly reduces the expression of several adipocyte-specific genes, including PPARα and PPARγ target genes, partly due to an increase in nuclear factor kappa B (NFκB) activity and subsequent induction of interleukin-6[44], therefore explaining at least part of its effects on glucose and lipid metabolism. Trans-10,cis-12 CLA inhibits insulin-stimulated glucose uptake and oxidation, reduces fatty acid uptake and alters fatty acid metabolism in differentiating human preadipocytes[37].

MI-CLA appears to increase energy expenditure in rodents by several mechanisms that are not fully understood, although an increase in uncoupling protein UCP1 and UCP3 gene expression does not seem to be involved[4,15,16,45,46]. However, some studies show an increase in UCP2 expression (mostly with trans-10,cis-12 CLA supplementation) in brown and white adipose tissue and skeletal muscle[39,47,48].

Table 2 Effects of trans-10,cis-12 CLA on adipocytes

Effect	Potential mechanism
↓ lipid uptake	↓ SCD[34,35] and LPL[10,36,37]
↓ glucose uptake	↓ GLUT4[37–38]
↑ fatty acid oxidation	↑ CPT[10]
↓ lipogenesis	↓ SREBP-1[39]
↑ apoptosis	↑ TNFα?[39]
↑ energy expenditure	↑ UCP2?[39,47,48]
differentiation?	↑ NFκB?
lipolysis?	↓ PPAR target genes?[44]

CLA – conjugated linoleic acid; SCD – stearoyl-CoA desaturase; LPL – lipoprotein lipase; GLUT4 – glucose transporter-4; CPT – carnitine palmitoyltransferase; SREBP-1 – sterol regulatory element-binding protein-1; TNFα – tumour necrosis factor alpha; UCP2 – uncoupling protein 2; NFκB – nuclear factor kappa B; PPAR – peroxisome proliferator-activated receptor. ↑ – increase; ↓ – decrease; ? – possible.

According to all these data, it seems that trans-10,cis-12 CLA elicits its de-lipidative activity through both metabolism and cell cycle control. More research is necessary to clarify conflicting results and differences between species.

Potential effects of CLA on adipocytes are summarised in Table 2.

Effects of conjugated linoleic acid on the liver and skeletal muscle

Several *in vivo* and *in vitro* studies in mice have reported an increase in both liver fatty acid synthesis and oxidation in response to MI-CLA supplementation[39,49–51]. CLA may mediate its effects through PPARα and PPARβ/δ (both trans-10,cis-12 and cis-9,trans-11 CLA isomers are their ligands[52]), a decrease in SCD-1[53] expression and other alternative pathways, as suggested by studies on knock-out mice[54,51]. However, there seem to be differences between species, as hamsters[55] on a CLA-supplemented diet developed liver hypertrophy but not lipid accumulation, and rats or pigs fed with CLA-enriched diets showed no changes in weight or lipid content in the liver[4].

There is evidence of the anabolic properties of CLA on lean mass in mice[10], and probably in other species[56,57]. However, the effects of CLA on the skeletal muscle are still unclear. CLA-fed mice showed an increase of CPT activity on skeletal muscle, improving β-oxidation[10] and, as previously indicated, an enhancement in UCP2 expression is also evident in some studies.

Metabolic effects of conjugated linoleic acid

The effects on lipid metabolism of trans-10,cis-12 CLA, the active isomer involved in fat mass loss, are currently objects of concern. Administration of trans-10,cis-12 CLA to humans results in an increase of the LDL/HLDL ratio[24], some studies reflecting an increase in LDL-cholesterol[29], while others showing a decrease in HDL-cholesterol[29,30,33,58]; however, such effects are just marginal and

not statistically significant compared to the control group in some of the studies[29,33]. These deleterious effects are not evident with the administration of MI-CLA or the cis-9,trans-11 isomer[24,25,31,58–60]. Moreover, cis-9,trans-11 CLA actually appears to decrease LDL cholesterol in humans[24,30]. A 6.4 g day^{-1} MI-CLA doses for 12 weeks produced a modest increase in lean mass (0.6 kg) but significant decrease in serum HDL-cholesterol, sodium, hemoglobin, and hematocrit, and significant increases in serum alkaline phosphatase, C-reactive protein, and K-6, and white blood cells.

Plasma triacylglycerides (TAG) did not significantly change or decrease compared to placebo in some studies with MI-CLA supplementation[33,59,62,63]. Nevertheless, in another study mean plasma TAG concentration was higher during supplementation with a mixture 85% trans-10,cis-12 CLA than with another mixture 80% cis-9,trans-11 CLA[24].

Interestingly, there is no clear dose–response relationship in the relative hyperlipidemic properties of trans-10, cis-12 CLA and hypolipidemic properties of cis-9,trans-11 CLA in humans[24], suggesting that this influence could be exerted even at low doses[24]. Moreover, in apolipoprotein E knockout mice, supplementation with trans-10,cis-12 CLA had a profound pro-atherogenic effect, whereas cis-9,trans-11 CLA impeded the development of atherosclerosis[64].

In a similar way, there are conflicting results related to carbohydrate metabolism in humans. Although several studies show that neither cis-9,trans-11 CLA nor trans-10,cis-12 CLA supplementation significantly modify plasma glucose or insulin levels or alter insulin sensitivity (revised QUICKI) or insulin resistance (HOMA-IR)[24,29,59], Riserus *et al.*[31,58,65] repeatedly report marginal but detrimental effects of both trans-10,cis-12 CLA (3.4 g day^{-1}) and cis-9,trans-11 CLA (3 g day^{-1}) on insulin sensitivity (measured as the insulin sensitivity index with the euglycemic clamp) and lipid peroxidation in obese subjects with metabolic syndrome. Another study in type 2 diabetic patients supplemented with MI-CLA (3 g day^{-1}) also shows unfavourable effects on fasting glucose, insulin resistance (HOMA) and oral glucose insulin sensitivity[60]. These results are in agreement with those of CLA-fed mice[39], but not with the reported improvement on insulin sensitivity of some other studies in genetically obese mice[66] or Zucker rats supplemented with CLA[12].

Conclusions

Although there is evidence in animals of the ability of trans-10,cis-12 CLA to reduce adiposity and increase lean mass, such unequivocal data supporting the efficacy of either of the CLA isomers in humans are not available.

Moreover, contradictory results raise concern about the possibility of the deleterious effects of trans-10,cis-12 CLA on the lipid profile, glucose metabolism and insulin sensitivity. Therefore, it is advisable to consider with caution the use of CLA supplements containing high quantities of trans-10,cis-12 CLA, especially in obese patients with type 2 diabetes or metabolic syndrome, which constitutes a considerable proportion of the whole overweight/obese population.

Before CLA supplementation is recommended, further research on human effectiveness and safety of the different isomers of CLA is required.

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