CLA and Body Weight Regulation in Humans

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ABSTRACT: CLA comprises a group of unsaturated FA isomers with a variety of biological effects in experimental animals. CLA reduces body fat accumulation in animal models and has been suggested to have significant effects on lipid and glucose metabolism, e.g., antidiabetic effects in obese Zucker rats. It has been proposed that the *trans*10-*cis*12 isomer is the active isomer associated with the antiobesity and insulin-sensitizing properties of CLA. The metabolic effects in humans in general, and isomer-specific effects specifically, are not well characterized. In a series of controlled studies in humans, we investigated the effects of CLA (given as the commercially available mixture of isomers and as the purified *trans*10-*cis*12 CLA isomer) on anthropometry, lipid and glucose metabolism, and markers of lipid peroxidation. Preliminary results indicate that CLA may slightly decrease body fat in humans also, particularly abdominal fat, but there is no effect on body weight or body mass index. There is no simultaneous improvement in lipid or glucose metabolism. Rather, the *trans*10-*cis*12 CLA isomer unexpectedly caused significant impairment of the peripheral insulin sensitivity as well as of blood glucose and serum lipid levels. In addition, CLA markedly elevated lipid peroxidation. Thus, the metabolic effects of CLA in humans seem complex; further studies, especially of isomer-specific effects and for longer time periods, are warranted.

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CLA comprises a group of positional and geometric isomers of conjugated octadecadienoic acid, derived from linoleic acid (18:2n-6) and produced by bacterial biohydrogenation in the ruminant gut (1). In human food, CLA is derived mainly from dairy and ruminant meat sources (2). CLA is found in human serum lipids (3) as well as in other tissues including adipose tissue (4).

CLA has been shown to reduce body fat and increase lean body mass in growing animals by as yet unknown mechanisms (5–8). Recent data have shown beneficial effects of CLA on several components of the metabolic syndrome in Zucker diabetic fatty rats such as normalized glucose tolerance and reduced hyperinsulinemia; plasma levels of FFA (9) and a significantly improved blood lipid profile were reported in CLA-fed hamsters (10).

The metabolic syndrome represents a cluster of risk factors (insulin resistance, dyslipidemia, hypertension, and abdominal obesity) predisposing for coronary heart disease and type-2 diabetes (11). Abdominal visceral adiposity seems to be a key factor in the metabolic syndrome (12). The sagittal abdominal diameter (SAD) has been suggested to be the best simple anthropometric measurement of visceral fat (13) and is strongly associated with increased cardiovascular risk (14,15) and insulin resistance (16). Epidemiologic data from a population of elderly men showed an inverse correlation between the estimated dietary intake of milk fat and abdominal obesity (17), suggesting some indirect evidence for the postulated metabolic effects of CLA also in humans.

The antiobesity properties and metabolic effects of CLA have at present been studied mainly in animals and should therefore be tested also in humans. We performed a series of studies to investigate the effects of CLA, and of specific CLA isomers, on body composition and adiposity in humans. In addition, we investigated the effects of CLA on aspects of lipid and glucose metabolism as well as on markers for lipid peroxidation and inflammation. This paper reviews some of our studies and compares the results with those of other recent human studies with CLA.

Effects of CLA on body fat in humans. Although considerable data exist in growing animals indicating a reduced body fat accumulation after CLA, there have up to now been surprisingly few studies in humans. Nearly all of the studies have used commercially available mixtures of isomers, usually containing similar proportions of the *cis*9-*trans*11 and *trans*10-*cis*12 CLA isomers, or other preparations containing several CLA isomers. Table 1 summarizes present knowledge regarding effects of CLA on body mass index (BMI) and body fat in humans.

In a randomized, double-blind study, Atkinson (18) supplied obese people, who were instructed to follow a weight loss regimen with a reduction in calories and increase in exercise, with a mixture of CLA (2.7 g/d) or placebo for 6 mon. Both groups lost a similar amount of body weight and body fat and there was no significant difference between the groups, although a *post hoc* analysis suggested that there could have been a subpopulation in the CLA-fed group that gained lean body mass and lost body fat. In contrast, Blankson *et al.* (19) reported reductions in body fat in a randomized,

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Abbreviations: BMI, body mass index; PG, prostaglandin; SAD, sagittal abdominal diameter; UCP, uncoupling protein.

double-blind study of overweight or obese volunteers ($n = 47$). The subjects were divided into five groups receiving 1.7, 3.4, 5.1, or 6.8 g CLA or a control preparation (olive oil), respectively, for 12 wk. As in all other studies of supplementation with CLA in humans, there were no differences in body weight or changes in BMI, but there was a significantly higher reduction in body fat mass in the CLA groups as a whole compared with the placebo ($P < 0.03$). The reduction of body fat was significant for the 3.4- and 6.8-g CLA groups without any clear suggestion of a dose–response effect. The authors suggested that CLA may reduce body fat mass in humans and that no additional effect is achieved with doses >3.4 g CLA/d.

In a carefully performed study, Zambell *et al.* (20) investigated the effect of CLA supplementation on body composition and energy expenditure in healthy, normal-weight women. Women ($n = 17$) were confined to a metabolic suite in which diet and activity were controlled and held constant; they were fed either a CLA preparation or placebo for 64 d. Body composition was determined by total body electrical conductivity as well as by dual X-ray absorptiometry; energy expenditure, fat oxidation, and respiratory exchange ratio were measured. CLA had no significant effect on either body composition or energy expenditure. The amount of CLA given in this study was rather low, i.e., 2 g/d, with a mixture of different CLA isomers including 0.8 g/d of the two isomers *cis*9-*trans*11 and *trans*10-*cis*12 taken together.

Mougios and coworkers (21) examined the effect of CLA supplementation in healthy, normal-weight young women and men. In a placebo-controlled fashion, the study group consumed 0.7 g CLA/d for 4 wk followed by a second 4-wk period of consuming 1.4 g CLA/d. The proportion of body fat, estimated from the sum of 10 skinfold measurements, did not change significantly during the study compared with a control group.

We investigated the effects of supplementation with CLA, administered as the commercially available mixture of isomers or as a purified preparation of the *trans*10-*cis*12 CLA isomer, in humans. In a double-blind study, Smedman and Vessby (22) studied a group of healthy men and women ($n = 53$) given either a mixture of CLA containing 3.4 g CLA/d or a control preparation for 12 wk. There was a significant reduction in body fat by 3.8% ($P < 0.001$) in the CLA group. The body fat change, calculated from the three-compartment model based on caliper measurements of skinfold thickness and bioimpedance (23), was significantly different from that in the control group ($P = 0.050$). Body weight, BMI, and SAD were unchanged.

When giving the same amount and type of CLA preparation to a group of abdominally obese men during a 4-wk double-blind randomized study, Risérus *et al.* (24) demonstrated a significant mean decrease of the SAD by 0.6 cm ($P = 0.003$) in the CLA group compared with the control group ($P = 0.04$). There were also significant reductions of the waist/hip ratio and the waist circumference within the CLA group, but these changes were not significantly different from those of the control group.

The *trans*10-*cis*12 CLA isomer is suggested to have antiobesity and antidiabetic properties in animals. For the first time in humans, we were able to test a CLA preparation containing purified *trans*10-*cis*12 CLA and compare that with the conventional mixture of CLA isomers and a control preparation (25). This was again a trial in abdominally obese men with the metabolic syndrome; the goal was to determine whether CLA could improve insulin sensitivity, lipid metabolism, or body composition during a 3-mon treatment period. The amount of CLA ingested corresponded to 2 g/d, either as a mixture of the two main isomers or as purified *trans*10-*cis*12 CLA. At the end of the 3 mon, there were no significant differences between the groups associated with the changes in BMI, body fat, waist girth, or SAD. However, within the *trans*10-*cis*12 CLA group, there were significant reductions of BMI, waist girth, and body fat, whereas SAD and body fat decreased within the CLA group. SAD tended to decrease ($P = 0.07$) after both CLA treatments compared with the control group.

Effects of CLA on lipid and glucose metabolism in humans. In contrast to some of the animal studies, it has not been possible to show any improvement of the metabolic status in humans after supplementation with CLA. On the contrary, the *trans*10-*cis*12 CLA isomer induced insulin resistance in abdominally obese men with the metabolic syndrome (25), resulting in simultaneously increased glycemia and reduced concentrations of HDL cholesterol. The impairment of insulin sensitivity may be an isomer-specific effect. The CLA mixture did not significantly affect glucose metabolism but lowered HDL cholesterol. A significant reduction in HDL cholesterol after supplementation with CLA was noted also in other controlled studies (19,21), and Medina *et al.* (26) reported a tendency to increased insulin levels in plasma after CLA supplementation.

Effects of CLA on antioxidants and lipid peroxidation in humans. CLA is easily oxidized, and it has been suggested that increased lipid oxidation may contribute to the antitumorigenic effect demonstrated in experimental studies (27,28). When given to humans, CLA induces lipid peroxidation (29,30), as indicated by significantly increased levels of urinary 8-iso-prostaglandin (PG) $F_{2\alpha}$, a major F_2-isoprostane, and 15-keto-dihydro $PGF_{2\alpha}$, a major metabolite of $PGF_{2\alpha}$, which are direct measurements of nonenzymatic (31) and enzymatic (32) lipid peroxidation *in vivo*, respectively. F_2-isoprostanes are probably the most reliable and clinically relevant markers of oxidative stress available (33). Both inflammation (34) and oxidative stress (35) have been suggested to contribute to insulin resistance. The increased lipid peroxidation may also be an isomer-specific effect.

The lipid peroxidation after CLA ingestion disappears rapidly when CLA supplementation is interrupted (24). No reductions in antioxidant capacity or in the levels of plasma tocopherols have been demonstrated (29,30). The mechanisms behind the increased lipid peroxidation after CLA and their clinical importance are currently under investigation.

DISCUSSION

There is no evidence from any human studies that supplementation with CLA would reduce body weight or BMI. Although

TABLE 1
Effects on Body Weight and Body Fat of CLA: Human Studies[a]

Reference number	CLA[b] dose (g)	Participants			Effects on		
		n	Sex	BMI	BMI	% Body fat	SAD
18	2.7	2 × 40	M/W?	Obese	0	0	NM
19	1.7–6.8	5 × 12	M/W	28–30	0	Reduction	NM
20	0.8 (several isomers)	7/10	W	23	0	0	NM
21	0.7–1.4	10/12	M/W	23	0	0	NM
24	3.4	10/15	M	32	0	NM	Reduction
22	3.4	24/26	M/W	25	0	Reduction	0
25	2.0	3 × 20	M	30–31	0	0	0 (—)

[a]Abbreviations: BMI, body mass index; SAD, sagittal abdominal diameter; M/W, men/women; NM, not measured.
[b]Sum of CLA isomers *c*9-*t*11 and *t*10-*c*12.

not convincingly shown in all studies, there is a suggestion of an effect on body fat, and possibly especially on abdominal fat, by CLA in several studies (Table 1). A significant body fat reduction was not found in humans with CLA doses <3 g/d. However, in a study in overweight subjects, there was no clear evidence of a dose–response effect (19), and no further reduction of body fat was seen when the CLA dose was >3.4 g/d. A reduction in abdominal fat was demonstrated in obese men after only 4 wk of CLA supplementation (24), and it has not yet been shown that the putative effect of CLA on body fat increases with time. A certain reduction in body fat has been indicated in both normal-weight and obese subjects.

The lack of an effect in some of the studies might be due to the small numbers of participants and the rather large measurement errors in determining body composition in humans. Quite clearly, the effect on body fat, if any, is moderate and not accompanied by any metabolic improvement. It is too early to speculate whether there is an isomer-specific effect on body composition also in humans.

The mechanism behind a possible reduction in body fat by CLA is not known. CLA has been suggested to affect the rate of *de novo* lipogenesis and/or the rate of lipolysis. Increased lipolysis and decreased lipoprotein lipase activity have been observed *in vitro* in adipocytes when CLA was added to the medium (36). Reduced production of antilipolytic PG in adipose tissue has been suggested as a cause for increased lipolysis (37). One might postulate that dietary supplementation with CLA, as a possible inducer of catecholamine-related lipolysis, could cause a selective reduction in visceral fat, indirectly measured as a reduction in SAD. A possible thermogenic effect of CLA is suggested by tissue analyses of uncoupling protein (UCP) expression in prediabetic CLA-fed rats, which showed an increased expression of brown adipose tissue UCP-2 mRNA compared with control rats (38).

Supplementation with the *trans*10-*cis*12 CLA isomer led to a tendency toward reduced abdominal fat coinciding with significantly impaired insulin sensitivity, increased fasting glucose, and dyslipidemia—an apparently paradoxical result. This suggests that the metabolic effects of CLA in humans are different from those reported in diabetic Zucker rats (9) but are in agreement with the effects in female C57BL/6J mice, which became severely insulin resistant and lipodystrophic after CLA supplementation (39). Similarly, male AKR/J mice showed signs of insulin resistance after CLA (40). An intriguing possibility is that CLA, and possibly the *trans*10-*cis*12 isomer specifically, induces adipocyte apoptosis, with reduction of the fat mass and an induction of insulin resistance. The *trans*10-*cis*12 CLA isomer may also inhibit the formation of new, small, insulin-sensitive fat cells, possibly *via* downregulation of peroxisome proliferator-activated receptor γ (39). Reduced activity of lipoprotein lipase, as shown *in vitro* (36), might also contribute to reduced fat accumulation with a concomitant impairment of serum lipid levels owing to decreased clearance of VLDL TG.

Although the putative reduction of body fat, and possibly mainly of abdominal fat, would suggest a positive metabolic effect of CLA, the metabolic impairment after supplementation with the *trans*10-*cis*12 isomer, i.e., a significantly impaired insulin sensitivity, is cause for concern. Estimated from dose–response clamp studies in obese subjects and lean controls (41), the relative decrease of insulin sensitivity after *trans*10-*cis*12 CLA was equivalent to having an excess body weight of ~15 kg, at a current mean weight of ~100 kg, indicating a rather powerful effect of this isomer. The amounts of *trans*10-*cis*12 in the diet (in which the major isomer is *cis*9-*trans*11) are very low, but commercial CLA mixtures do contain 20–45% *trans*10-*cis*12, indicating that long-term use of these preparations may be of concern. However, more clinical trials over longer time periods are required to make firm conclusions regarding the effects of CLA and different CLA isomers on body composition and metabolism as well as on the clinical safety of (specific isomers of) this FA. Specifically, it would be interesting to determine whether other CLA isomers have other effects and whether CLA supplementation may prevent weight regain, in line with the reduced body fat accumulation in animals. This could be tested, e.g., after a period of body weight reduction or in connection with smoking cessation.

SUMMARY

Preliminary results indicate that CLA may slightly decrease body fat in humans, particularly abdominal fat, but that there is no simultaneous reduction of body weight or improvement

of lipid or glucose metabolism. Rather, the *trans*10-*cis*12 isomer unexpectedly caused significant impairment of peripheral insulin sensitivity as well as of blood glucose and serum lipid levels. In addition, CLA markedly elevated lipid peroxidation. The mechanism behind these changes is at present unknown. Importantly, the safety of CLA supplements should be evaluated more closely because a large number of people are currently using commercially available CLA preparations as antiobesity agents. Thus, the metabolic effects of CLA in humans seem complex, and further studies, especially of isomer-specific effects and for prolonged time periods, are warranted.

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