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The effects of t10,c12 CLA isomer compared with c9,t11 CLA isomer on lipid metabolism and body composition in hamsters☆

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Abstract

The objective of the present study was to examine the effects of two different isomers of conjugated linoleic acid (CLA), c9,t11 CLA and t10,c12 CLA, compared with linoleic acid (LA) used as control, on body composition, lipoprotein profile, hepatic lipids and fecal fat content in hamsters. Animals were assigned to the three diet groups ($n=15$) during 28 days. The diet was composed of 2% of the experimental fat, and throughout the experimental protocol, the hamsters experienced similar food intake. No significant differences were noted in body weight gain among the three diet groups. However, the t10,c12 CLA-fed animals showed higher low-density lipoprotein cholesterol (LDL-C) concentrations (0.9±0.1 mmol/L) than those who ingested either LA (0.6±0.1 mmol/L) or c9,t11 CLA isomer (0.7±0.1 mmol/L), although the t10,c12 CLA consumption decreased hepatic cholesterol and triglycerides and increased fecal fat content compared with the other two groups. Under the present experimental conditions, the dietary c9,t11 CLA isomer showed no positive beneficial effect on plasma lipids. Furthermore, the t10,c12 CLA isomer induced undesirable higher LDL-C, although it reduced hepatic lipids and fat digestibility in hamsters.

Keywords: Conjugated linoleic acid; Isomers; Lipoproteins; Lipid metabolism; Body composition; Hamsters

1. Introduction

Conjugated linoleic acid (CLA) is produced either naturally from linoleic acid (LA) in the rumen of bovine animals by fermentative bacteria or endogenously in lactating dairy cows by delta-9 desaturase of *trans*-11 octadecanoic acid [1], or chemically by biohydrogenation [2] and alkali isomerization of LA [3]. In food, CLAs are mainly found in dairy products and ruminant meats, such as beef and lamb, which contain approximately 80% c9,t11 CLA and 10% t10,c12 CLA isomers [4].

CLA has attracted high interest over the past decade because of their multiple biological effects. Among them, these fatty acids have been shown to reduce body fat accumulation, and to lower blood lipids and atherogenic risk in animal studies. Early work indeed demonstrated that CLA reduces adiposity in growing mice, where 6-week-old ICR mice were fed a diet containing less than 1% CLA for 28–32 days [5]. Further work in various animal models confirmed those findings [6]. Feeding nonobese mice with CLA reduced some depots of fat mass, specifically retroperitoneal and epididymal white adipose tissue masses and brown adipose tissue [7], which might be more sensitive to CLA-mediated effects. In addition, feeding rabbits with atherogenic diet CLA mixture results in less early aortic atherosclerosis [8] or in regression of preexisting atherosclerosis [9]. Feeding different levels of CLA (0.06%, 0.11% and 1.1%) to hamsters led to lower plasma total cholesterol, very low-density lipoprotein (VLDL) plus low-density lipoprotein cholesterol (LDL-C) and triglyceride

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Table 1
Fatty acid composition of the experimental fats[a]

Fatty acid	Experimental fat (%)		
	LA	c9,t11 CLA	t10,c12 CLA
16:0	0.1	<0.1	<0.1
18:0	0.4	<0.1	<0.1
c9 18:1	5.3	3.3	0.9
c9,c12 18:2	93.0	0.6	<0.1
t10,c12 18:2	–	0.8	91.0
c9,t11 18:2	–	92.4	4.8
Other isomers 18:2[b]	<0.1	3.0	3.3

[a] Provided by Natural ASA.
[b] Principally *cis-cis* 9,11 and 10,12 plus *trans-trans* 9,11 and 10,12.

concentrations [10]. An isomer-specific effect of CLA has been also observed when t10,c12 CLA was much more effective at lowering LDL-C and high-density lipoprotein cholesterol (HDL-C) than c9,t11 CLA in hamsters [11] and lowering adipose tissue mass than c9,t11 CLA in mice [12]. However, CLA does not appear to produce identical results in all studies. For example, pigs fed with 1% mixed CLA isomers for 6 weeks as part of an isoenergetic diet showed no change in heat production, energy retention or body weight and a trend toward increased levels of triglycerides and VLDL and LDL-C, without distinct changes in the HDL fraction [13]. Sugano et al. [14] also found no differences in serum total cholesterol or HDL-C in rats fed with diets containing 1% CLA. Thus, different studies proved different results owing to the fact that different experimental conditions were used such as age, dose, duration of the study, animal species, food consumption and initial metabolic status.

In the present study, we examined the effects of the individual c9,t11 CLA isomer and t10,c12 CLA isomer compared with LA on body composition, blood lipid profile and fecal fat content under similar food intake among the hamsters. LA was the reference fatty acid, since it has well-recognized lowering effect on plasma lipids [15]. We hypothesized that the t10,c12 CLA isomer as compared to LA and the c9,t11 CLA isomer would induce beneficial effects on lipid metabolism and body composition under controlled physiological feeding conditions in hamsters. The hamster model was chosen because of its established responsiveness to plasma cholesterol lowering and anti-atherogenic interventions [16–18].

2. Materials and methods

2.1. Diets

Two CLA isomers were tested in the present study, c9,t11 CLA and t10,c12 CLA, in comparison with LA. The individual isomers of CLA and LA were purchased from Natural ASA (Hovdebygda, Norway). The composition of the three experimental fatty acid sources is shown in Table 1.

The composition of the experimental diets (EDs) is given in Table 2. All the added ingredients of the three diets were supplied by ICN Biomedical (Aurora, OH), except for lard, which was purchased from local supermarket. AIN-93G mineral mixture and AIN-93-VX vitamin mixture were used in the present study. Moreover, as proposed by Reeves et al. [19], BHT was added to minimize the oxidation of the fatty acids. Each diet was formulated to be isoenergetic, isolipidic and isonitrogeneous. The energy content of the diets was measured in an automatic adiabatic calorimeter (Model 1241, Parr Instruments, Moline, IL). Energy values were between 4.67 and 4.73 kcal/g. The protein content of each diet (N×6.25) was assayed by Leco FP-528 (ISO 34/SC 5, Principle of Dumas). Protein values were 21.0% (w/w) for LA, 21.0% (w/w) for c9,t11 CLA and 20.8% (w/w) for t10,c12 CLA. The lipid content of each diet was measured by Manual Soxtec System HT6 (Tecator, Hoganas, Sweden). Lipid values were 12.5% (w/w) for LA, 12.6% (w/w) for c9,t11 CLA and 12.1% (w/w) for t10,c12 CLA. Dry matter of each diet was also measured by Fisher Econo Temp Laboratory Oven Model 30G. Percentage of water obtained from the samples was between 6% and 6.5% (w/w).

2.2. Experimental animals

Forty-five growing hamsters (Charles River laboratories) weighing 50–60 g on arrival where housed individually in plastic cages placed in a room controlled for constant temperature (20±2°C) and humidity (45–55%), and kept under a daily light–dark cycle (0900 to 2100 h). Following a 6-day adaptation period to the animal quarters where animals were fed a ground nonpurified commercial diet (NPD) (Purina, St. Louis, MO), hamsters were then divided into three dietary groups on the basis of their body weight and food intake (n=15 per group), prior to the 28-day experimental period. They were then gradually transferred to their respective purified diet differing in lipid source by feeding a mixture of ground NPD and experimental diet over a 5-day period (25% ED/75% NPD for 1 day, 50% ED/50% NPD for 2 days and 75% ED/25% NPD for 2 days). Experimental diets and tap water were provided ad libitum

Table 2
Composition (w/w) of the three experimental purified diets

Ingredient	%
Casein	23
DL-Methionine	0.3
Cornstarch	38.2
Sucrose	15
Lard	10
CLA or LA	2
Cellulose	5
Minerals AIN-93	3.5
Vitamins AIN-93VX	1
CaHPO4	1.5
Choline bitartrate	0.2
Cholesterol	0.3
BHT	0.002

BHT, butylated hydroxytoluene.

Table 3
Mean food intake and body weight of male hamsters fed with the three purified diets for 28 days

	LA	t10,c12 CLA	c9,t11 CLA
Mean food intake (g/d)	6.7±0.2	6.8±0.1	6.9±0.2
Initial body weight (g)	68±1	70±2	69±2
Final body weight (g)	98±3	101±2	101±2
Body weight gain (g)	30±2	31±1	32±2

Values are mean±S.E.M (n=15 animals). Diets were similar in content, except for the source of fat: LA or CLA having different isomerization.

for 28 days. Records of food intake and body weight were taken everyday in the morning. Food intake was recorded by subtracting the weight of the stainless steel box from the total weight of the box plus the fresh food. Then the box was firmly fixed to the cage. A small square stainless steel wire mesh was inserted in the box to prevent the hamsters from spreading their feed in their beddings. This protocol was approved by the Animal Care Committee of Laval University according to the guidelines of the Canadian Council on Animal Care.

At day 0, before the experimental diet was given to the hamsters and after 28 days on their respective experimental diets, they were weighed and anesthetized with isoflurane after a 12-h fast, body composition was analyzed using a Piximus apparatus (Lunar, Madison, WI), and the body fat and lean mass were measured with the help of X-ray from the sternum to the tail of the hamster. All measurements were taken when the hamsters were on front in the Piximus apparatus.

On days 18–20, hamsters were transferred to individual stainless steel wire bottom mesh cages, and feces were collected, weighed and stored at −80°C for lipid extraction using the Manual Soxtec System HT6.

2.3. Laboratory analyses

After 28 days on experimental diets and after 12-h fast, blood samples were collected by cardiac puncture in tubes containing disodium EDTA (0.05%). Animals were then sacrificed by asphyxia with CO_2. Epididymal tissue was cut off and weighed. Liver lobs were removed, weighed, frozen in liquid nitrogen and stored at −80°C until the extraction of hepatic lipids. The blood samples were centrifuged at 2500 rpm for 10 min in order to isolate the plasma. An aliquot of plasma was frozen at −80°C for total lipid determinations.

The next day after blood sampling, lipoproteins were separated from fresh plasma by ultracentrifugation (TL-100 Tabletop Ultracentrifuge, Beckman, Palo Alto, CA) at 100 000 rpm and 15°C for 120 min, using a TLA-100.4 rotor. The plasma samples were adjusted to a density of 1.063 g/ml by the addition of a solution of NaBr-NaCl 1.478 g/ml [20]. A two-step density gradient was formed by layering the density-adjusted plasma underneath NaCl solution (d=1.006 g/ml) [20]. Consequently, plasma lipoproteins were fractionated into triglyceride-rich lipoproteins [chylomicrons and VLDLs (d<1.006 g/ml), LDLs (1.006<d<1.063 g/ml) and HDLs (1.06<d<1.21 g/ml]. To facilitate the visualization of the single lipoprotein bands after centrifugation, Coomassie blue (5% w/w) was added to the plasma samples before ultracentrifugation. Plasma cholesterol and triglycerides were measured in these lipoproteins as well as in the fresh plasma using the enzymatic Triglycerides/GB and CHOD-PAP kits (Roche Diagnostics, Laval, Quebec). Phospholipids in plasma were determined using Phospholipids B Enzymatic Colorimetric Method (Wako Chemicals USA).

Hepatic lipids were extracted with chloroform/methanol (2:1, v/v) using the method of Folch et al. [21]. Triglycerides and cholesterol were determined by enzymatic kits as described above.

Feces were lyophilized and ground. Fat content in feces was determined by extraction with anhydrous diethyl ether (Soxtec System HT6 Extraction Unit; Tecator) after acid hydrolysis (4M HCL) for 30 min (Soxtec System 1047 Hydrolysing Unit; Tecator) [22].

2.4. Statistical analysis

Data were subjected to an analysis of variance (ANOVA) using the Statistical Analysis System (SAS

Table 4
Plasma lipids of male hamsters fed with the three purified diets for 28 days

Plasma lipids	LA	t10,c12 CLA	c9,t11 CLA
Total cholesterol (mmol/L)	5.3±0.3	5.6±0.3	5.1±0.3
VLDL cholesterol (mmol/L)	1.9±0.2	1.6±0.2	1.9±0.1
LDL-C (mmol/L)	0.6±0.1^b	0.9±0.1^a	0.7±0.1^b
HDL-C (mmol/L)	3.0±0.2	3.1±0.1	3.0±0.1
Total triglycerides (mmol/L)	2.6±0.2	2.6±0.1	2.6±0.2
VLDL triglycerides (mmol/L)	2.5±0.3	2.3±0.2	2.3±0.2
LDL triglycerides (mmol/L)	0.05±0.01	0.07±0.01	0.04±0.01
HDL triglycerides (mmol/L)	0.1±0.01	0.1±0.01	0.1±0.01
Total phospholipids (mmol/L)	3.9±0.2	4.2±0.3	4.1±0.2

Values are mean±S.E.M. (n=15 animals). Diets were similar in content, except for the source of fat: LA or CLA having different isomerization. Mean values within a row not sharing a common superscript were significantly different (P<.05).

Table 5
Liver weight and hepatic lipids of male hamsters fed with the three purified diets for 28 days

	LA	t10,c12 CLA	c9,t11 CLA
Liver weight (g)	4.8±0.2	5.4±0.1	5.1±0.1
Hepatic triglyceride concentrations (μmol/g)	7.2±0.8^a	2.9±0.3^b	8.2±0.9^a
Total hepatic triglycerides (μmol)[1]	32±4^a	15±2^b	41±4^a
Hepatic cholesterol concentrations (μmol/g)	83±4^a	48±3^b	89±5^a
Total hepatic cholesterol content(μmol)[2]	393±31^a	256±20^b	446±23^a

Values are mean±S.E.M. (n=15 animals). Diets were similar in content, except for the source of fat: LA or CLA having different isomerization. Mean values within a row not sharing a common superscript were significantly different (P<.05).

[1] Hepatic triglyceride concentrations×Liver weight.
[2] Hepatic cholesterol concentrations×Liver weight.

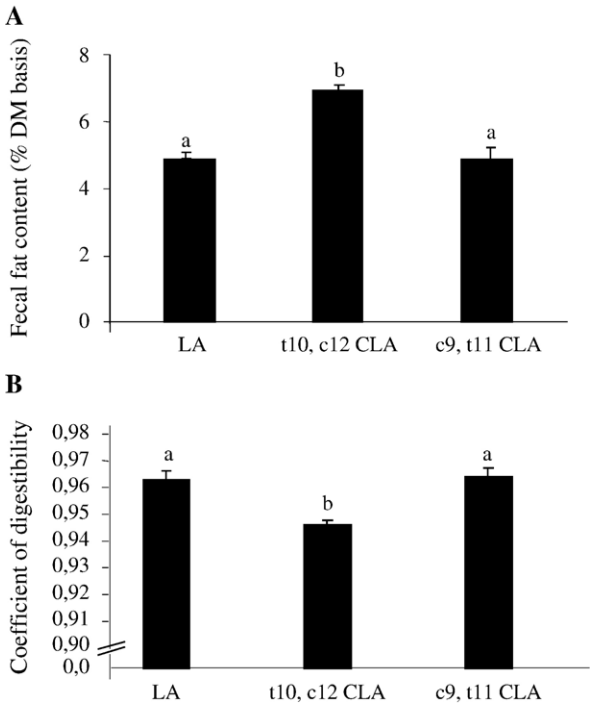

Fig. 1. (A) Fecal fat content in hamsters fed with the three experimental diets for 28 days. Columns not showing a common superscript were significantly different ($P<.05$). (B) Coefficient of digestibility in hamsters fed with the three experimental diets for 28 days. Columns not showing a common superscript were significantly different ($P<.05$).

Institute, Cary, NC) general linear model (GLM) procedure in order to determine the main diet effects. Diet effects detected by ANOVA at a probability level inferior to .05 were then submitted to a Tukey's studentized range (HSD) test in order to identify differences among diet groups. Data on plasma and hepatic triglyceride and cholesterol concentrations as well as different lipoprotein fractions and fecal fat content are presented in tables and figure as the untransformed means±S.E.M. However, data on fecal fat content were transformed by log 10 prior to statistical analysis in order to make comparisons among homogeneous and normal means. Pearson correlation coefficients were used to quantify the univariate associations among variables.

3. Results

3.1. Food intake and body weight

No significant difference in food intake was observed among the three dietary groups. Furthermore, the growth rate was comparable among the three groups, and this was confirmed by the lack of significant difference in body weight gain ($P=.46$), as shown in Table 3.

3.2. Plasma lipids

The total plasma cholesterol, triglyceride and phospholipid concentrations were similar between the three dietary groups (Table 4). No significant differences were noted in plasma VLDL cholesterol and triglycerides, LDL triglycerides nor in HDL-C and HDL triglycerides. However, t10,c12 CLA showed highest LDL-C values compared with either LA or c9,t11 CLA.

3.3. Hepatic lipids

Hamsters fed with t10,c12 CLA isomer showed lower hepatic cholesterol and triglyceride concentrations than those with the two other dietary groups. Moreover, liver weight tended to be higher with t10,c12 ($P=.06$) as compared to LA and c9,t11. These results are presented in Table 5.

3.4. Fecal fat content

Higher fecal fat content was noted in t10,c12 CLA than in the other two groups (Fig. 1A). To take into account fat intake in addition to fecal fat, a coefficient of digestibility was calculated [(fat intake − fat excreted)/fat intake] during the three days of fecal collection, and consequently, t10,c12 CLA had the lowest coefficient of digestibility (Fig. 1B).

3.5. Body composition

Body composition of hamsters was determined after the period of adaptation, that was on Day 0, before the beginning of the experimental protocol as well as after 28 days of experimental diets. In accordance to our selection criteria, on Day 0, hamsters weighed around 60–80 g. After the experimental protocol, they weighed around 90–110 g. No differences for lean mass, fat mass, total (fat+lean) mass, percentage of fat, bone mass content and bone mass density

Table 6
Body composition of male hamsters on Day 0 and on Day 28

	Day 0			Day 28		
	LA	t10,c12 CLA	c9,t11 CLA	LA	t10,c12 CLA	c9,t11 CLA
Lean body mass (g)	52±1	52±1	52±1	73±2	76±2	74±2
Body fat mass (g)	11±0.4	12±1	11±1	21±1	20±1	21±1
Total (fat+lean) (g)	63±1	64±2	63±2	93±3	96±2	94±2
Percentage body fat (%)	18±1	18±1	17±1	22±1	21±1	22±1
Bone mass content (g)	0.8±0.1	0.8±0.02	1.1±0.3	1.5±0.03	1.5±0.04	1.5±0.04
Bone mass density (g/cm^2)	0.01±0.001	0.05±0.001	0.05±0.001	0.1±0.001	0.1±0.001	0.1±0.002
Epididymal fat tissue (g)	ND	ND	ND	2.1±0.2	2.2±0.1	2.2±0.1

Values are mean±S.E.M. ($n=15$ animals). Diets were similar in content, except for the source of fat: LA or CLA having different isomerization. ND, not determined.

were found among the three groups, neither on Day 0 nor on Day 28 (Table 6). Furthermore, there was no significant effect of the three experimental CLA diets on epididymal fat pads (Table 6).

4. Discussion

The results of the present study provide information regarding the impact of t10,c12 and c9,t11 CLA isomers on plasma lipoproteins and body composition in hamsters under controlled feeding conditions. Previous data have demonstrated that t10,c12 CLA can lower LDL-C in hamsters [11] and body fat in mice [12] concomitantly with a decrease of food intake and/or body weight [11,12]. Our data indicate that t10,c12 CLA has the detrimental capacity to increase LDL-C levels, while having no effect on food intake, body composition nor body fat in hamsters, and although t10,c12 CLA isomer as compared to LA and c9,t11 CLA isomer lowered fat absorption and hepatic lipids. This result on LDL-C does not support our hypothesis that the t10,c12 CLA isomer would induce beneficial effects on lipid metabolism and body composition under controlled feeding conditions. Potential explanations for increased plasma LDL-C could include decreased LDL receptor activity, reduced fractional clearance rate of LDL in circulation or less affinity of LDL particles present into the circulation with LDL receptors in hamsters fed with t10,c12 CLA than those fed with c9,t11 CLA or LA. Further research is required to study LDL receptor activity following t10,c12 CLA feeding compared with LA and c9,t 11 CLA.

Previous study has identified the t10,c12 isomer, rather than the c9,t11 isomer, as being responsible for the biological effects on plasma lipids and body composition [11]. In the present study, c9,t11 had indeed no effect on plasma lipids, whereas the individual t10,c12 CLA isomer increased LDL-C. A recent study in healthy humans who received highly enriched doses of c9,t11 and t10,c12 CLA preparations also showed higher LDL/HDL-C ratio during t10,c12 CLA supplementation than during c9,t11 CLA supplementation, with no significant change in body composition by either isomer of CLA [23]. Thus, the present results do not confirm the beneficial lowering effects of t10,c12 CLA isomer on plasma total cholesterol and LDL-C previously observed in hamsters by De Deckere et al. [11]. In the latter study, the t10,c12 CLA isomer lowered plasma lipids partly as a result of a decreased energy intake or decreased body weight [11]. Therefore, the present data in hamsters indicate that in isoenergetic conditions, the individual t10,c12 CLA isomer may increase plasma LDL-C compared to the individual c9,t11 CLA isomer and LA.

There is also evidence that feeding CLA may affect liver metabolism in mice [24]. In the present study, we observed a strong tendency (P=.06) for t10,c12 to increase liver weight. This was however not accompanied by a higher level of lipids in the liver, as found in mice [7,25]. In previous studies, the t10,c12 CLA isomer has also been shown to increase liver weight, independent of body weight [11] or body fat [26]. De Deckere et al. [11] observed that increased liver weight was due to hypertrophy. Possible mechanisms by which t10,c12 CLA exerted lowering effect on hepatic lipids are that this isomer may reduce lipogenic enzymes that control lipogenesis and triglyceride esterification, or increase basal lipolysis leading to a decrease in triglyceride content, as already proposed by Evans et al. [27]. In this respect, De Deckere et al. [11] suggested that t10,c12 CLA can stimulate higher oxidation rate in vivo, in comparison to c9,t11 CLA. Interestingly, isolated perfused livers from rats fed 1% CLA mixture for 2 weeks produced significantly more ketones compared to livers from 1% LA-fed rats [28]. In the latter study, the ratio of β-hydroxybutyrate to acetoacetate was also increased, suggesting that dietary CLA may exert a hypolipidemic effect in the liver by increasing β-oxidation of fatty acids at the expense of fatty acid esterification.

Another possibility to explain the hypolipidemic effect of t10,c12 CLA in the liver is via a reduction of intestinal fat absorption, as estimated by a higher content of fecal fat and a lower coefficient of digestibility observed in this study. These results suggest that the specific structure of t10,c12 CLA may have lower affinity for the intestinal fatty acid-binding protein compared to those of LA and c9,t11 CLA, leading to a reduction in intestinal fat digestibility and absorption. Our results on fat absorption are in good agreement with those of Yeung et al. [29] showing a reduction of cholesterol absorption and a down-regulation of intestinal acyl-CoA cholesterol acyltransferase (ACAT) activity, an enzyme involved in the esterification and storage of intestinal cholesterol.

The present study showed no significant difference concerning body weight and composition among the three experimental diets. These results on body weight are in good agreement with those obtained by Yeung et al. [29] and Bouthegourd et al. [30] using 10% lard plus 2% CLA and 12.5% fat, of which beef tallow was the main source, plus 0.6% CLA, respectively. On the other hand, Nicolosi et al. [10] and Gavino et al. [31] who incorporated 10–11% coconut oil as the main source of fat plus 1% CLA reported that diets supplemented with CLA induced significantly lower body weight gain than control diet in hamsters. The present results therefore suggest that the effects of CLA on body weight and composition might depend either on the source of fat used in the diet or on the strain of hamsters. It might be possible that lard, which is the main source of fat used in the present study, may not promote as much as coconut oil the reducing effect of CLA on body fat accumulation. There is also a possibility that our strain of hamster was not as responsive to CLA feeding as other strains of Syrian hamsters. Furthermore, the present results support the concept that body composition of hamsters is less responsive to CLA treatment than that of mice. Indeed, West et al. [32] found that CLA reduced body fat in male

AKR/J mice fed with either a high-fat diet (45% of calories) or a low-fat diet (15% of calories) by increasing energy expenditure.

In conclusion, t10,c12 CLA appeared to be a physiological active CLA isomer regarding lipid metabolism, whereas the c9,t11 CLA isomer had little or no effect on lipid metabolism in hamsters. Nevertheless, under isoenergetic conditions, the incorporation of t10,c12 CLA isomer into the diet in the present study caused an increase in plasma LDL-C, although hepatic lipids and fat digestibility were reduced when compared with LA and c9,t11 CLA isomer. No effect was observed on body composition. The present results may suggest that reduced hepatic lipid concentrations following ingestion of t10,c12 CLA isomer could be a consequence of decreased intestinal fat digestibility and absorption and possibly increased lipolysis in the liver rather than in the adipose tissue under isoenergetic conditions in the hamster. Therefore, the results of this study show no positive beneficial effect of supplementing diets with either c9,t11 or t10,c12 CLA isomer on the blood lipid risk factors for cardiovascular diseases. More work is needed on the mechanisms of t10,c12 CLA to better understand its effects on plasma and hepatic lipids, and on fat digestibility and absorption.

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