Conjugated linoleic acid does not affect digestion and absorption of fat and starch—a randomized, double-blinded, placebo-controlled parallel study

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Abstract

Objective: Conjugated linoleic acid (CLA) is known as a potent agent for altering body weight and composition. However, its effect on the process of digestion is still unknown. The aim of this study has been to elucidate the effect of a 3-month supplementation with CLA on starch and fat digestion and absorption in humans. Approach: The study included 74 obese and overweight adults who were randomized to receive 3.0 g of CLA or sunflower oil as placebo daily for 3 months. Digestion and absorption of fat and starch was assessed using non-invasive breath tests with a stable¹³C isotope (cumulative percentage dose recovery, CPDR) before and after the supplementation period. To exclude the effect of oxidation, in addition total energy expenditure (TTE) was measured by a ¹³C bicarbonate breath test. Results: The changes in CPDR values (ΔCPDR median (interquartile range)) were no different between subjects from the CLA group and the placebo group (fat: −0.2 (−9.1–4.1) versus 0.6 (−7.0–8.0), p < 0.4796; starch: −1.3 (−9.5–2.4) versus −1.0 (−5.1–1.7), p < 0.5520, respectively). The incidence of negative and positive values of ΔCPDR was no different between groups [for fat: 53.1% versus 46.7%, RR 1.195, 95% CI 0.804–1.882] and for starch: 67.7% versus 56.7%, RR 1.195, (95% CI 0.804–1.777)]. The changes in TTE did not differ between the CLA and the placebo group (respectively 1 (48; 267) versus −8 (−120;93) kcal; p < 0.2728). Conclusion: Supplementation with CLA for 3 months did not affect fat and starch digestion assessed by ¹³C mixed triglyceride breath test and ¹³C starch breath test.

Introduction

Excess weight and obesity is the consequence of a long-term positive energy balance that is frequently related with excessive intake of saturated fat or simple carbohydrates. The state of being overweight or obese leads to serious health implications such as type 2 diabetes mellitus and cardiovascular disease. Therefore, new therapeutic options for successful body mass reduction and maintenance of the obtained effects are needed. Conjugated linoleic acids (CLA) have recently gained much interest as a promising supplement for improving body weight and composition [1].

CLA, a polyunsaturated fatty acid, is known for its anti-carcinogenic and anti-atherogenic properties [1]. CLA is made by bacteria in the process of linoleic acid isomerization or desaturation of 11-trans octadecenoic acid [2]. CLA constitutes a mixture of geometric and positional isomers of linoleic acid, of which the most prevalent in the diet is cis-9, trans-11 octadecadienoic acid, and the less frequent is the trans-10, cis-12 isomer. These two isomers can be found in commercially available CLA products; however, the anti-obesity effect is attributed to the trans-10, cis-12 isomer [3].

Numerous animal studies indicate that CLA influences body composition. Most researchers found that...
CLA decreases body fat; however, the results differ between species [4–6]. The evidence from randomized clinical trials proves that long-term CLA supplementation causes weight loss in humans, but of minor clinical relevance (at most 5% of baseline weight) [1, 7]. Other research shows that CLA supplementation reduces fat mass, although these studies have varied with regard to the dose, the type of isomer, and study duration [8, 9]. Therefore, as to the purported benefits of CLA in humans, the results are contradictory. Nevertheless, CLA has been reported to play a beneficial role in lipid metabolism via the activation of enzymes such as lipoprotein lipase and carnitine-palmitoyl-transferase-1. Its supplementation reduces lipogenesis and enhances the lipolysis and β-oxidation of fatty acids in animal models [10, 11]. CLA may also inhibit the differentiation of adipocytes and prevent fatty acid accumulation in adipose tissue [10, 12]. Studies on animals and humans report inconsistent results regarding CLA’s impact on glucose homeostasis [13]. CLA supplementation seems to have no effect on glucose or insulin levels, purportedly because of transient metabolic changes [14–16].

Many potential effects of CLA have been studied to date; however, no data regarding its influence on fat and starch digestion or absorption are so far available. Therefore, the aim of our study is to evaluate its impact in overweight and obese subjects using the reliable methods of 13C mixed triglyceride (MTG-BT) and starch 13C breath test (S-BT).

Methods

Study population

The study comprised 74 adults with BMI ≥ 25 kg m⁻². Volunteers were recruited in The Obesity and Overweight Treatment Clinic of Poznań University of Medical Sciences, Poznań, Poland. The eligibility criteria included females over 18 years old and BMI ≥ 25 kg m⁻². The exclusion criteria were as follows: chronic systemic disease (excluding hypertension), gastrointestinal diseases (e.g. celiac disease), type 2 diabetes mellitus, and pregnancy. Before the study commenced, subjects were examined by a physician. Subjects who used CLA and other dietary supplements (green tea, mulberry leaves, chitosan, phaseolamin, prebiotics and probiotics) and medications (e.g. orlistat, metformin, acarbose) interfering with fat and starch digestion and/or absorption within the preceding month were also excluded. Subjects were instructed to maintain habitual diets. Diets were recorded before and during the intervention period. Energy and macronutrient intake was calculated to assure the subjects did not change their eating habits.

Randomization and blinding

The protocol of the study was previously described by Madry et al [17]. Subjects were assigned to receive placebo or CLA by a nurse unrelated to the study, according to a computer-generated randomization list (block size = 6) generated by an independent researcher. The study was conducted in parallel design with an allocation ratio of 1:1. No changes to methods were made after the trial’s commencement. To implement the random allocation sequentially numbered containers were used. All personnel (investigators, care givers, assessors and data analyst) involved in the study and all participants were unaware of the study group assignments until the end of the study.

Intervention

Each participant from the CLA subgroup was given 3.0 g of 80% CLA (50:50 trans-10, cis-12 isomers and cis-9, trans-11) daily for 3 months. Women were instructed to administer two capsules of the provided product three times a day with a meal. Likewise, volunteers from the placebo group consumed capsules containing 3.0 g of sunflower oil per day. Both intervention products were in identical transparent capsules packed in similar blisters. The intervention product was kindly provided by a pharmaceutical company (Olimp Laboratories, Dębica, Poland).

Outcome measures

Evaluation of fat and starch digestion as well as absorption was performed using a MTG-BT and S-BT, respectively. We assumed that the cumulative percentage dose recovery (CPDR) values reflected the process of digestion and absorption [18]. For the assessment of the changes in fat and carbohydrate digestion and absorption, the difference of CPDR after and before the supplementation period (ΔCPDR) was calculated. To evaluate total energy expenditure (TEE) a 13C bicarbonate breath test (B-BT) was performed [kcal/day].

MTG-BT procedure

The test was carried out after overnight fasting. Each of the study participants received a test meal containing 150 mg of 13C mixed triglyceride and 12.5 g of butter (fat content: 82%) mixed on a roll (50 g). Breath samples were obtained at baseline (fasting) and at half hour intervals (6 h) after ingestion of the test meal [19].

S-BT procedure

The baseline breath sample was obtained after an overnight fast. Afterwards, subjects received test meals containing naturally 13C-rich cornflakes (50 g) with low-fat milk (100 ml). Breath samples were obtained fasting (baseline) and every 30 min up to 4 h after the test meal [20, 21].
**B-BT procedure**

In the TEE assessment a dose of 50 mg of $^{13}$C bicarbonate was administrated orally after dissolution in about 125–150 ml of warm fruit tea. Breath samples were acquired from each subject over a total timespan of 3 h [22].

Breath tests were performed before and after the 3-month CLA or placebo supplementation period. The subjects did not receive either CLA or a placebo to the test meal. Both tests were performed one week apart. The subjects avoided eating food naturally abundant with $^{13}$C (kiwi fruit, pineapple, cane sugar,
The level of the statistical significance before and after the supplementation period.

Table 2. Values of cumulative percentage dose recovery (CPDR) after mixed triglyceride breath test for placebo and conjugated linoleic acid (CLA) intervention before (pre) and after 3 months of supplementation (post).

|          | CLA                  | Placebo               | p value |
|----------|----------------------|-----------------------|---------|
|          | Median (1st–3rd quartile) Mean ± SEM | Median (1st–3rd quartile) Mean ± SEM |         |
| Pre      | 22.6 (14.0–29.8) 23.3 ± 1.9 | 21.3 (15.1–25.7) 20.0 ± 1.6 | 0.3337  |
| Post     | 20.9 (17.4–25.8) 22.1 ± 1.6 | 20.0 (16.3–25.7) 21.1 ± 1.6 | 0.6393  |
| p value  | 0.5372               | 0.7711                |         |

Table 3. The increment values of cumulative percentage dose recovery (CPDR) after mixed triglyceride breath tests for conjugated linoleic acid (CLA) and placebo.

|          | CLA                  | Placebo               | p value |
|----------|----------------------|-----------------------|---------|
|          | Δ CPDR               |                       |         |
|          | Median (1st–3rd quartile) | Mean ± SEM |         |
| CLA      | –0.2 (−9.1–4.1) 0.6 (−7.0–8.0) | 0.4796 |         |
| Placebo  | −1.2 ± 1.8           | 1.2 ± 2.0             |         |

The level of the statistical significance before and after the supplementation period.

The values of CPDR before and after supplementation in the groups receiving the CLA intervention and placebo did not differ significantly (table 2). The changes in CPDR values (ΔCPDR median [interquartile range]) were no different between subjects from the CLA and placebo groups (table 3). The incidence of negative and positive values of ΔCPDR was no

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|          | Median (1st–3rd quartile) | Mean ± SEM |         |
| CLA      | –0.2 (−9.1–4.1) 0.6 (−7.0–8.0) | 0.4796 |         |
| Placebo  | −1.2 ± 1.8           | 1.2 ± 2.0             |         |

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**Table 4.** The number of subjects with positive and negative values of changes in cumulative percentage dose recovery (CPDR) after the mixed triglyceride breath test for conjugated linoleic acid (CLA) and placebo group.

| Group          | Negative ΔCPDR (% of subjects with negative ΔCPDR) | Positive ΔCPDR (% of subjects with negative ΔCPDR) | Relative risk (95% CI)* | p value  |
|----------------|-----------------------------------------------------|---------------------------------------------------|-------------------------|----------|
| CLA group (n = 32) | 17 (53.1)                                           | 15 (46.9)                                          | 1.1384 (0.6889–1.8822) | 0.6130   |
| Placebo group (n = 30) | 14 (46.7)                                           | 16 (53.3)                                          |                         |          |

*CI denotes confidence interval.

**Table 5.** The values of cumulative percentage dose recovery (CPDR) in starch breath test for placebo and conjugated linoleic acid (CLA) intervention before and after 3 months of supplementation.

| Group          | Median (1st–3rd quarter) | Mean ± SEM | P value  |
|----------------|--------------------------|------------|----------|
| CLA  | 14.2 (12.1–18.5) | 15.2 ± 1.0 | 0.0919   |
| Placebo  | 13.7 (12.1–17.5) | 15.0 ± 1.2 | 0.6518   |

| Group          | Median (1st–3rd quarter) | Mean ± SEM | P value  |
|----------------|--------------------------|------------|----------|
| CLA  | 11.5 (9.3–17.6) | 12.5 ± 1.2 | 0.2369   |
| Placebo  | 13.4 (11.9–17.7) | 14.0 ± 1.1 |          |

The effect of CLA in humans is still widely disputed[2]. Onakpoya et al revealed that long-term CLA intake significantly reduced body weight and, to a lesser extent, body fat, as compared to placebo[7]. Similarly, Whigham et al showed a modestly significant fat loss in 15 eligible trials[1].

According to various research studies, the safe CLA dose ranges from 3 to 6 g per day. In our study, we used 3 g of CLA, which is comparable to most studies[24–26]. Blankson et al proved that a higher amount (>3.4 g CLA per day) does not imply better weight reduction results[27]. The study evaluated the effect of a 12-week CLA intake on a similar study group using four various doses of CLA (1.7, 3.4, 5.1 or 6.8 g) and with olive oil as a placebo (9 g). Significant differences in the reduction of body mass were obtained only in the groups assigned to receive 3.4 g and 6.8 g of CLA, but the study included additional physical activity concomitant to the study; thus, it is difficult to discern the real influence of CLA.

The results of animal studies assessing different stages of fat metabolism are inconclusive[28, 29]. In vivo fatty acids β-oxidation could be evaluated by carnitine-palmitoyltransferase activity (CPT). CPT is a

**Discussion**

The effect of CLA in humans is still widely disputed worldwide. Herein, we attempt to elucidate for the first time the impact of a 3-month intake of CLA on metabolism of fat and starch. This study indicates that CLA does not exert any significant effect in this respect.

Previous investigations differ widely in their designs. The dosage, composition as well as duration of the CLA treatment, as well as subjects’ health conditions may considerably affect the study outcomes in humans. A meta-analysis by Onakpoya et al revealed that long-term CLA intake significantly reduced body weight and, to a lesser extent, body fat, as compared to placebo[7]. Similarly, Whigham et al showed a modestly significant fat loss in 15 eligible trials[1].

Different between the subgroups studied (table 4). The incidence of decreased digestion and absorption was no different in subjects in the CLA subgroup compared with those of the placebo subgroup (53.12% versus 46.67%, RR 1.1384, 95% CI 0.6889 to 1.8822).

**S-BT**

The level of starch digestion and absorption was reflected by the CPDR values. The values of CPDR before and after supplementation in groups receiving CLA intervention and placebo did not differ significantly (table 5). The changes in CPDR values (ΔCPDR median [interquartile range]) were no different between subjects from the CLA and the placebo groups (table 6). The incidence of negative and positive values of ΔCPDR was no different between the subgroups studied (table 7). The incidence of decreased digestion and absorption was no different between participants from the CLA subgroup and participants from the placebo subgroup (67.74% versus 56.67%, RR 1.1954, 95% CI 0.8044 to 1.7765).

**B-BT**

The TEE before and after supplementation in the CLA and placebo groups did not differ (table 8). No changes in TEE (Δ) were observed between subjects from CLA and placebo groups (table 9).
Table 7. The number of subjects with positive and negative values of changes in cumulative percentage dose recovery (CPDR) in starch breath test for placebo and conjugated linoleic acid (CLA).

|                      | Negative ΔCPDR (% of subjects with negative ΔCPDR) | Positive ΔCPDR (% of subjects with positive ΔCPDR) | Relative risk (95% CI) | p value |
|----------------------|----------------------------------------------------|----------------------------------------------------|------------------------|---------|
| CLA group (n = 31)   | 21 (67.7)                                          | 10 (32.3)                                          | 1.1954 (0.8044–1.7765) | 0.3722  |
| Placebo group (n = 30)| 17 (56.7)                                         | 13 (43.3)                                         |                        |         |

*CI denotes confidence interval.

Table 8. The values of total energy expenditure [kcal/day] measured by 13C bicarbonate breath test before and after 3-month intervention.

|          | CLA | Placebo | p value |
|----------|-----|---------|---------|
| Median (1st–3rd quartile) | | |
| Pre      | 2503 (2248–2650) | 2454 ± 42 | |
| Post     | 2522 (2392–2593) | 2514 ± 38 | |
| Mean ± SEM | | | 0.2170 |

Table 9. The values of changes in total energy expenditure measured by 13C bicarbonate breath test for conjugated linoleic acid (CLA) and placebo group.

|                      | Δ Total energy expenditure (kcal/day) | p value |
|----------------------|--------------------------------------|---------|
|                      | CLA | Placebo | |
| Median (1st–3rd quartile) | | | 0.2729 |
| Mean ± SEM             | 1 (–48; 267) | –8 (–120; 93) | |
|                      | 60 ± 36 | –18 ± 38 | |

mitochondrial rate limiting enzyme controlling the β-oxidation process. Rahman et al indicated that a 4-week intake of CLA increased CPT in a non-insulin-dependent diabetes mellitus model (perirenal fraction of visceral-adipose tissue, red gastrocnemius muscle, liver, brown adipose tissue) [28]. The study used a homogenate fraction of different tissues to represent overall fatty acid oxidation. Martin et al, however, documented that a 6-week diet containing 1% of CLA did not affect β-oxidation in skeletal and cardiac muscles [29]. Based on another mice model it was suggested that CLA (in the form of free fatty acids as well as triacylglycerols) may promote a mild increase in energy expenditure, while increased energy losses in excreta reflect decreased nutrient absorption [30, 31].

Assuming that both effects are present in humans, one could expect unchanged breath test results in this study. However, in that case it should be accompanied by weight losses in the CLA group, which were not observed in our trial [17]. To exclude the effect of oxidation, in this study we performed B-BT, which is a non-invasive and reliable method providing results in accordance with indirect calorimetry as the gold standard [32, 33]. We did not observe any differences in TEE changes in the course of CLA supplementation. Reports on different animal models raise a question as to which species mimic the human model best and what is the appropriate CLA dose per kg of body weight [30, 31, 34], which in animal models is far higher. Our results suggest that the impact of CLA on metabolic processes in humans remains unclear.

The present study attempts to assess the impact of 3-month CLA intake on starch and fat digestion and the subsequent absorption using a valid method of MTG-BT and S-BT. The method uses molecules of two stearic acids and 13C octanoic acid to serve as a labelled tracer through the process of hepatic β-oxidation and formation of 13CO2. During the 6 h of the test procedure, the dose of 13C recovered in the exhaled air is registered as a measure of intestinal lipolysis [35]. The other method, S-BT, measures CO2 in breath that comes from metabolized glucose previously hydrolyzed from starch [36]. Our study used cornflakes as a test meal. Starch from corn is digested in the small intestine, absorbed, then metabolized in the liver and transported to the lungs. No data are available referring to the impact of long-term CLA supplementation on carbohydrate digestion and absorption in humans so far. Some studies indicate that CLA can improve glucose tolerance and balance hyperinsulinemia in the animal model (obese-diabetic insulin resistant, prediabetic animals on a high-fat diet) [37, 38]. The study by Farina et al documented that CLA increases glucose oxidation and also enhances glucose uptake as well as incorporation into the rat muscle [39]. On the other hand, serum glucose levels have not changed in any of the animal studies [40–42].

The limitations of the study include the potential lack of full patients’ compliance, which we tried to minimize. The participants were called on the phone three times during the 3 months to provide motivation and ensure the subjects follow the regime. Additionally, women were asked to bring empty packages and to maintain a 90 day calendar to monitor the supplementation. Other limitations involve the fact that gut
microbiota was not assessed and that some of the patients consumed fermented foods during the study (fermented dairy products, sauerkraut). Nevertheless, these constituted a subject’s typical diet, which was the same for all groups studied and was unaltered throughout the study period. Lastly, our results are applicable only to women who also meet the inclusion and exclusion criteria of this trial. MTG-BT and S-BT were created to assess digestion and absorption, however the potential influence of other processes, e.g. liver metabolism and gastric emptying, cannot be excluded. Therefore further studies are needed to confirm the present findings.

Conclusions

Numerous studies have attempted to elucidate the effect of CLA. The results of our study, which is a randomized, placebo-controlled, double-blind nutritional intervention, indicate that 3-month CLA intake apparently does not influence digestion or absorption of either fat or starch in overweight and obese humans. Although this subject needs further investigation.

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Author contributions

JW, EM & AL designed the experiment; KM, AG, PB, EFW, MS, ICS, AMC & AL performed the research; JW supervised the study; JW, KM, AG & AL created database and analyzed data; JW, AG, KM & AL wrote the manuscript; EM & PB provided revisions. All authors reviewed and approved the manuscript.

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