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ORIGINAL PAPER

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CONJUGATED LINOLEIC ACID SUPPLEMENTATION AND GLUCOSE, INSULIN, LIPID, AND ADIPOKINE LEVELS IN OVERWEIGHT AND OBESE WOMEN – A RANDOMISED CONTROLLED TRIAL

Małgorzata Jamka[1], Klaudia Malikowska[2], Edyta Mądry[3], Patrycja Krzyżanowska-Jankowska[1], Ida Malesza[1], Katarzyna Jończyk-Potoczna[4], Judyta Cielecka-Piontek[5], Jarosław Walkowiak[1]✉, Aleksandra Lisowska[6]

[1]Department of Pediatric Gastroenterology and Metabolic Diseases, Poznan University of Medical Sciences
Szpitalna Str. 27/33, 60-572 Poznań, **Poland**
[2]Faculty of Health Sciences, Calisia University
Kaszubska Str. 13, 62-800 Kalisz, **Poland**
[3]Department of Physiology, Poznan University of Medical Sciences
Święcickiego Str. 6, 61-781 Poznań, **Poland**
[4]Department of Pediatric Radiology, Poznan University of Medical Sciences
Szpitalna Str. 27/33, 60-572 Poznań, **Poland**
[5]Department of Pharmacognosy and Biomaterials, Poznan University of Medical Sciences
Rokietnicka Str. 3, 60-806 Poznań, **Poland**
[6]Department of Pediatric Diabetes, Auxology and Obesity, Poznan University of Medical Sciences
Szpitalna Str. 27/33, 60-572 Poznań, **Poland**

ABSTRACT

Background. Many studies have examined the effect of conjugated linoleic acid (CLA) on cardio-metabolic parameters, but their findings have been inconsistent. However, only a few have explored the impact of CLA supplementation on adipokine levels. Therefore, this study aims to investigate the effect of CLA supplementation on glucose, insulin, lipid, and adipokine levels in overweight and obese women.

Material and methods. 74 overweight or obese women were recruited and randomly assigned to either the CLA or control group. The intervention group received six CLA capsules daily (each containing 0.5 g of an 80% 50:50 mixture of cis-9, trans-11 and trans-10, cis-12 isomers) for 12 weeks, and the control group received sunflower oil capsules for the same 12-week duration. Fasting glucose and insulin levels, lipid profiles, adiponectin, apelin, ghrelin, leptin, omentin, resistin, and visfatin concentrations, as well as a homeostatic model assessment of insulin resistance (HOMA-IR), were measured before and after the intervention period.

Results. The CLA intervention significantly decreased leptin levels ($p = 0.034$) and increased the HOMA-IR index ($p = 0.041$) and ghrelin concentrations ($p = 0.043$). No differences were observed between groups in glucose, insulin, and lipid parameters, but a significant difference was noted in visfatin levels (median [interquartile range]: 0.43 (–1.56; 1.76) vs. –0.39 (–1.91; 0.77) ng/ml, $p = 0.046$).

Conclusion. In conclusion, our results do not support the health-promoting effects of CLA supplementation in overweight and obese women. The study protocol was retrospectively registered in the Deutsche Register Klinischer Studien (DRKS) database (DRKS-ID: DRKS00010462) on 04/05/2016.

Keywords: CLA, obesity, glucose and insulin homeostasis, lipid profile, adipokine

✉jarwalk@ump.edu.pl, https://orcid.org/0000-0001-5813-5707

INTRODUCTION

Overweight (body mass index (BMI): 25.0–29.9 kg/m^2) and obesity (BMI $\geq$ 30 kg/m^2) are global health problems, defined as abnormal or excessive fat accumulation in humans. These conditions can affect anyone, regardless of sex, age, or race (World Health Organization, 2024). Overweight and obesity are major risk factors for several noncommunicable diseases, including certain types of cancer, such as breast, ovarian, endometrial, prostate, liver, gallbladder, kidney, and colon cancer (World Cancer Research Fund and American Institute for Cancer Research, 2018). They are also strongly linked to type 2 diabetes mellitus (Narayan et al., 2007), cardiovascular diseases (Powell-Wiley et al., 2021), and musculoskeletal disorders (Wearing et al., 2006). Globally, excessive body weight contributes to over four million deaths each year (Afshin et al., 2017). As the primary cause of obesity is excessive energy intake relative to energy expenditure, diet and physical activity are the most effective methods for managing body weight (Olateju et al., 2023). However, alternative approaches are still being sought.

Conjugated linoleic acid (CLA) refers to a group of positional and geometric isomers of linoleic acid containing conjugated double bonds, predominantly found in dairy products and ruminant meat (Chin et al., 1992). The most representative CLA is cis-9, trans-11 isomer (Pariza et al., 2001), which is formed through bacterial biohydrogenation of linoleic acid in the rumen of ruminants. Additionally, synthetic forms of CLA are available, produced during the catalytic production of vegetable oils and the thermal processing of food. These synthetic CLA isomers typically consist of a mixture of isomers, such as cis-9, trans-11, and trans-10, cis-12 (Seles, 2014).

CLA has been shown to possess anti-obesity, anti-adipogenic (Whigham et al., 2007) and anticancer (Miri-Lavasani et al., 2022) properties. Some studies have also examined the effect of CLA supplementation on adipokine levels, although the results have been contradictory (Gaullier et al., 2007; Ghobadi et al., 2019; Mohammadi-Sartang et al., 2018; Von Frankenberg et al., 2014). There is evidence suggesting that CLA may have an antidiabetic effect (Ryder et al., 2001) and could potentially modulate lipid metabolism (Moloney et al., 2004). However, other studies indicate that CLA might create a prediabetic state, reduce insulin sensitivity, promote insulin resistance (Moloney et al., 2004; Risérus et al., 2004), and increase cholesterol levels (Asbaghi et al., 2022). Different CLA isomers may have contrasting effects on human health. For instance, Brown et al. (2001) suggested that the trans-10, cis-12 isomer, rather than the cis-9, trans-11 isomer, may attenuate lipogenesis. Similarly, Tricon et al. (2004) found that the trans-10, cis-12 isomer might positively affect blood lipids, in contrast to the cis-9, trans-11 isomer. On the other hand, Tholstrup et al. (2008) showed that a mixture of the trans-10, cis-12, and cis-9, trans-11 isomers had a more negative effect on lipid profiles, lipid peroxidation, and oxidative stress compared to the naturally occurring cis-9, trans-11 isomer.

This study aims to evaluate the effect of CLA on glucose metabolism, insulin sensitivity, lipid metabolism, and adipokine levels in overweight or obese women. These parameters were chosen for their central roles in metabolic health and cardiovascular function. Adipokines, including adiponectin, apelin, ghrelin, leptin, omentin, resistin, and visfatin, are key mediators in the cross-talk between adipose tissue and metabolic homeostasis. These hormones play a crucial role in managing biological functions within adipose tissue and facilitating communication between adipose tissue and other organs. Consequently, disturbances in adipokine secretion have been linked to the development of several metabolic disorders, such as obesity, diabetes, and cardiovascular diseases. Adipokines are widely recognised for their role in modulating inflammation, controlling food intake, regulating body weight, and enhancing insulin sensitivity. Furthermore, they have a crucial impact on the cardiovascular system. These diverse roles highlight the importance of adipokines in maintaining metabolic and physiological balance (Hemat Jouy et al., 2024). This research was motivated by conflicting findings on CLA's effects on cardio-metabolic parameters and the limited number of studies evaluating the impact of CLA intake on adipokine levels.

MATERIALS AND METHODS

Study Design

This parallel randomised controlled trial was conducted between July 2014 and May 2015. The study protocol

was registered in the Deutsche Register Klinischer Studien (DRKS) database (DRKS-ID: DRKS00010462, registration date: 04/05/2016, German Clinical Trials Register, 2016) and received approval from the Poznan University of Medical Sciences Bioethics Committee (ref. 606/12, 453/13, 358/14 and 398/15). The study adhered to the standards outlined in the Declaration of Helsinki (Sawicka-Gutaj et al., 2022) and the manuscript was prepared following the Consolidated Standards of Reporting Trials (CONSORT) guideliness (Moher et al., 2010). All participants received detailed study information and provided written informed consent prior to enrolment.

As described previously (Dus-Zuchowska et al., 2016; Łochocka et al., 2014; Madry et al., 2016; Mądry et al., 2020; Walkowiak et al., 2017), participants were screened at the Department of Internal Medicine, Metabolic Disorders and Hypertension, Poznan University of Medical Sciences, Poland. The inclusion criteria were: women, aged > 18 years old, overweight or obese (BMI ≥ 25 kg/m^2), and with stable body weight (± 3 kg within the past three months). Exclusion criteria were: a history of chronic systemic diseases (excluding hypertension), type 2 diabetes mellitus, liver or pancreatic diseases, celiac disease, previous treatment with CLA or agents affecting fat digestion or absorption (e.g., chitosan, orlistat, or green tea), pregnancy and breastfeeding.

Participants Flow

A total of 187 subjects were screened in the Department of Internal Medicine, Metabolic Disorders and Hypertension at Poznan University of Medical Sciences, Poland. Of these, 81 participants met the inclusion criteria. However, seven women declined to participate due to the following reasons: lack of free time (3 subjects), difficulty cooperating (1 subject), suspected ovarian tumour (1 subject), personal problems (1 subject), and diarrhoea (1 subject).

Ultimately, 74 women were randomly assigned to either the intervention group (n = 37) or the control group (n = 37). Of these, 61 women completed the study: 31 from the intervention group and 30 from the control group. In the intervention group, six participants discontinued the study due to absence at scheduled visits (4 participants), pregnancy (1 participant), and nausea (1 participant). In the placebo group, seven participants dropped out due to absence at scheduled visits (4 participants), nausea (2 participants), and a rash (1 participant). The participant flow is shown in Figure 1.

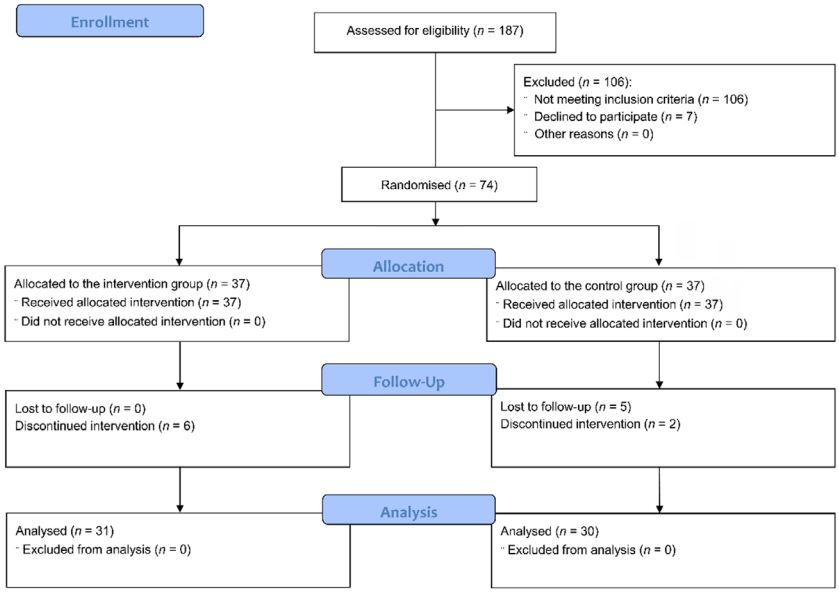

Fig. 1. Study flow chart

Baseline characteristics of the study population are presented in Table 1. Compared to earlier publications (Dus-Zuchowska et al., 2016; Łochocka et al., 2014; Mądry et al., 2020; Walkowiak et al., 2017), one additional participant was excluded from the analysis due to missing biochemical analysis.

Table 1. Baseline characteristics of the study population

	CLA group (n = 37)		Control group (n = 37)		*p*
	Mean ±SD (95%CI)	Median (IQR)	Mean ±SD (95%CI)	Median (IQR)	
Age, years	52 ±10 (48; 55)	54 (43; 59)	51 ±13 (47; 55)	55 (45; 61)	0.808
BMI, kg/m^2	34.38 ±4.34 (32.93; 35.83)	34.00 (30.70; 37.58)	34.99 ±4.09 (33.63; 36.36)	35.36 (31.75; 38.60)	0.503
Glucose, mg/dl	95.64 ±14.31 (90.88; 100.42)	91.00 (87.00; 105.00)	95.08 ±14.02 (90.41; 99.76)	93.00 (84.00; 103.00)	0.729
Insulin, mU/l	15.33 ±6.36 (13.21; 17.45)	14.60 (11.00; 19.10)	16.83 ±7.90 (14.20; 19.47)	15.30 (10.90; 18.90)	0.574
HOMA-IR	3.64 ±1.68 (3.08; 4.2)	3.32 (2.17; 4.63)	4.07 ±2.37 (3.27; 4.86)	3.50 (2.42; 4.48)	0.677
TC, mg/dl	218.73 ±37.87 (206.10; 231.35)	209.00 (194.00; 253.00)	213.32 ±41.46 (199.50; 227.15)	217.00 (183.00; 238.00)	0.578
HDL-C, mg/dl	47.73 ±10.91 (44.09; 51.37)	47.00 (40.00; 55.00)	50.27 ±10.34 (46.82; 53.71)	50.00 (43.00; 56.00)	0.344
LDL-C, mg/dl	139.97 ±36.18 (127.91; 152.03)	136.00 (116.00; 165.00)	137.00 ±36.69 (124.77; 149.23)	136.00 (111.00; 158.00)	0.717
TG, mg/dl	142.00 ±52.23 (124.58 159.41)	143.00 (104.00; 171.00)	139.59 ±56.60 (120.72; 158.47)	132.00 (107.00; 156.00)	0.833
Adiponectin, µg/ml	7.40 ±3.41 (6.27; 8.54)	7.28 (4.80; 8.93)	7.12 ±4.07 (5.77; 8.48)	6.74 (5.09; 7.93)	0.420
Apelin, ng/l	92.73 ±70.31 (69.29; 116.18)	67.88 (37.44; 151.8)	81.03 ±63.61 (59.83; 102.24)	45.78 (37.81; 104.39)	0.627
Ghrelin, ng/ml	11.85 ±4.68 (10.29; 13.41)	11.65 (9.91; 13.23)	11.61 ±6.17 (9.56; 13.67)	11.19 (7.46; 13.64)	0.449
Leptin, ng/ml	22.17 ±11.80 (18.23; 26.1)	20.81 (14.13; 27.87)	23.92 ±11.50 (20.09; 27.76)	20.70 (15.63; 29.76)	0.545
Leptin/adiponectin	3.66 ±2.18 (2.93; 4.93)	3.33 (1.97; 5.09)	4.68 ±4.62 (3.13; 6.22)	3.26 (2.37; 5.42)	0.642
Omentin, ng/ml	278.67 ±87.79 (249.40; 307.94)	274.92 (214.52; 321.36)	256.01 ±94.85 (224.39; 287.63)	258.48 (180.72; 313.84)	0.256
Resistin, ng/ml	8.67 ±4.15 (7.29; 10.06)	7.46 (5.26; 11.38)	7.73 ±3.72 (6.49; 8.97)	6.44 (5.00; 9.64)	0.384
Visfatin, ng/ml	9.08 ±6.00 (7.08; 11.08)	8.22 (6.55; 9.59)	8.89 ±3.12 (7.85; 9.93)	8.46 (7.09; 9.63)	0.405

BMI – body mass index, HDL-C – high-density lipoprotein cholesterol, HOMA-IR – homeostatic model assessment of insulin resistance, IQR – interquartile range, LDL-C – low-density lipoprotein cholesterol, SD – standard deviation, TC – total cholesterol, TG – triglycerides, 95% CI – 95% confidence interval.

Interventions Protocol

Participants were randomly assigned to two groups: intervention and control. The intervention group received capsules containing CLA (0.5 g of 80% CLA containing a 50:50 mixture of cis-9, trans-11 and trans-10, cis-12 isomers), while the control group received capsules containing sunflower oil. All capsules were manufactured and supplied by Olimp Laboratories (Pustynia, Poland), designed to be identical in appearance, and packaged in identical blisters. The fatty acid composition of the CLA and placebo capsules is presented in Table 2.

Table 2. Comparison of fatty acids composition in CLA and placebo capsules

Fatty acids	CLA, %	Placebo, %
C16:0	3.6	4.8
C18:0	1.1	2.1
C18:1	12.9	10.2
C18:2	1.2	61.2
C18:3	0.8	21.7
C20:0	0.4	0.0
Isomer c9, t11 CLA	40.0	0.0
Isomer t10, c12 CLA	40.0	0.0

CLA – conjugated linoleic acid.

Participants were instructed to take six capsules daily (two capsules three times a day with main meals) for 12 weeks without altering their dietary habits or physical activity habits. The dose of CLA was chosen based on evidence from previous studies and is consistent with doses used in similar research (Carvalho et al., 2012; Eftekhari et al., 2014; López-Plaza et al., 2013; Medina et al., 2000; Noone et al., 2002; Steck et al., 2007). Furthermore, earlier studies confirmed that this dose is safe and does not increase the risk of adverse events (Berven et al., 2000; Iwata et al., 2007).

Compliance was monitored through monthly phone calls by the study team and by requiring participants to record pill intake on a calendar. To be included in the final analysis, participants needed to consume at least 75% of the supplements (391 capsules).

The study's primary outcome was to evaluate the intervention's effect on starch and lipid digestion using a starch breath test and a mixed triglyceride breath test (Walkowiak et al., 2017). This paper focuses on secondary outcomes, including the effects of CLA on glucose and insulin homeostasis, lipid metabolism, and adipokine levels. All assessments were performed at the Department of Pediatric Gastroenterology and Metabolic Diseases, Poznan University of Medical Sciences, Poland.

Anthropometric Parameters

Anthropometric parameters were measured with participants wearing light clothing and no shoes. Body weight and height were assessed using a medical scale with a stadiometer (Radwag, Random, Poland), with measurements taken to the nearest 0.1 kg and 0.5 cm, respectively. BMI was calculated using the standard formula based on weight and height, with overweight defined as BMI ≥ 25 kg/m^2 and obesity defined as BMI ≥ 30 kg/m^2 (World Health Organization, 2024).

Biochemical Markers

Fasting blood samples were collected in the morning after a 12-hour fast, following the last training session and meal. The samples were centrifuged and stored at –80°C until analysis. The following markers were measured before and after the intervention period: glucose, insulin, lipid profile, adiponectin, apelin, ghrelin, leptin, omentin, resistin and visfatin.

Glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) were measured in human serum using a Beckman Coulter AU analyser (Brea, CA, USA), with LDL-C estimated using the Friedewald formula (Friedewald et al., 1972). Insulin concentrations in human serum were determined using the Architect analyser (Abbott, Abbott Park, IL, USA), employing a chemiluminescent microparticle immunoassay.

The remaining parameters were measured using enzyme-linked immunosorbent assays (ELISA): Adiponectin (Mediagnost, Reutlingen, Germany); Human Apelin (Sun Red Biological Technology Co., LTD, Shanghai, China); Ghrelin Human EIA kit (Phoenix

Pharmaceuticals Inc., Burlingame, CA, USA); Leptin Sandwich (DRG Instruments GmbH, Marburg, Germany); Omentin-1 (DRG Instruments GmbH, Marburg, Germany); Resistin Recombinant Human (Phoenix Pharmaceuticals Inc., Burlingame, CA, USA); Visfatin, C-terminal (Phoenix Pharmaceuticals Inc., Burlingame, CA, USA).

Glucose, insulin, and lipid metabolism parameters were assessed at the Central Laboratory of Karol Jonscher's Pediatric Clinical Hospital, while adipokine levels were measured at the Laboratory of the Department of Pediatric Gastroenterology and Metabolic Diseases. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was calculated by multiplying fasting glucose [mg/dl] and insulin [mU/l] levels, then dividing by 405 (Matthews et al., 1985). Additionally, the leptin-to-adiponectin ratio was calculated.

Data Analysis

The American Diabetes Association recommendations were used to assess fasting plasma glucose concentrations, with impaired fasting glucose defined as fasting glucose levels between 100 and 125 mg/dl, and normal fasting glucose defined as levels ranging from 70 to 99 mg/dl (Elsayed et al., 2023). The reference range for fasting insulin was between 3 and 25 mU/l, and the cut-off for HOMA-IR to diagnose insulin resistance was ≥ 1.8 (Gayoso-Diz et al., 2013). According to the National Cholesterol Education Programme, total cholesterol (TC) levels should not exceed 200 mg/dl, while LDL-C and triglycerides TG should be lower than 130 mg/dl and 150 mg/dl, respectively. Furthermore, the recommended HDL-C concentration is > 40 mg/dl (National Cholesterol Education Program, 2002).

Randomisation and Blinding

Participants were randomly allocated to the intervention and control groups (allocation ratio: 1:1) using a computer-generated randomisation list. Blocking randomisation (block size = 6) was performed by an independent researcher, who concealed the allocation sequence until participant enrolment. The allocation was blinded to study participants, outcomes assessors, and statisticians.

Minimum Sample Size

The study is part of a larger project (Łochocka et al., 2014). The minimum sample size was determined based on the primary outcomes—starch and lipid digestion assessed using breath tests (Walkowiak et al., 2017)—and calculated with Statistica 13 PL software (TIBCO Software Inc., Palo Alto, CA, USA). To account for a potential dropout rate of 20%, a significance level of 5%, and a detection power of 80% ($\alpha = 0.05$, $\beta = 0.2$), the required sample size for each group was calculated to be 37 participants.

Using data from previous studies, we hypothesised that the mean differences would explain approximately 75% of the variances observed in earlier experiments (Lochocka et al., 2015). Additionally, the minimum sample size was recalculated based on the leptin-to-adiponectin ratio reported by MacRedmond et al. (2010), further confirming that 37 participants per group would be sufficient to detect significant differences between groups.

Statistical Analysis

Data analysis was conducted using the Statistica 13 PL software (TIBCO Software Inc., Palo Alto, CA, USA). The results are presented as mean, standard deviation (SD), 95% confidence interval (95% CI), median, and interquartile range (IQR, Q1–Q3). The normality of the data was assessed using the Shapiro-Wilk test. Differences between the study groups were analysed with the Mann-Whitney U-test, while intragroup changes from baseline were evaluated using the Wilcoxon test. A p-value of < 0.05 was considered statistically significant.

RESULTS

The effects of the intervention on glucose and insulin homeostasis, lipid metabolism, and adipokine levels are presented in Table 3. Following the intervention, homeostatic model assessment of insulin resistance HOMA-IR ($p = 0.041$) and ghrelin concentrations ($p = 0.043$) showed significant increases. In contrast, leptin levels ($p = 0.034$) significantly decreased in the CLA group (within-group effect), with no significant changes observed in the control group. Additionally, there were no significant differences between the effects of CLA and placebo on glucose, insulin, and lipid parameters. However, the intervention and control groups exhibited different effects on visfatin levels (between-group comparison: median [IQR] 0.43 (–1.56; 1.76) vs. –0.39 (–1.91; 0.77) ng/ml, $p = 0.046$).

Table 3. Effects of intervention on glucose and insulin homeostasis, lipid metabolism, and adipokine levels

	CLA group (n = 31)							Control group (n = 30)							
	Pre–intervention		Post–intervention		Δ		p^1	Pre–intervention		Post–intervention		Δ		p^1	p^2
	Mean ±SD (95%CI)	Median (IQR)	Mean ±SD (95%CI)	Median (IQR)	Mean ±SD (95%CI)	Median (IQR)		Mean ±SD (95%CI)	Median (IQR)	Mean ±SD (95%CI)	Median (IQR)	Mean ±SD (95%CI)	Median (IQR)		
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Glucose mg/dl	97.19 ±14.85 (91.74; 102.64)	92.00 (87.00; 107.00)	99.00 ±17.61 (92.54; 105.46)	95.00 (85.00; 107.00)	1.81 ±15.65 (–3.93; 7.55)	3.00 (–6.00; 12.00)	0.289	94.66 ±14.87 (89.12; 100.22)	94.50 (84.00; 103.00)	93.13 ±13.97 (87.91; 98.35)	94.00 (85.00; 98.00)	–1.53 ±10.33 (–5.39; 2.32)	–2.50 (–8.00; 7.00)	0.503	0.214
Insulin mU/l	15.05 ±6.50 (12.67; 17.44)	14.60 (9.20; 19.10)	16.41 ±7.29 (13.73; 19.08)	16.00 (11.80; 19.50)	1.35 ±4.60 (–0.33; 3.04)	2.00 (–1.20; 4.10)	0.124	17.37 ±8.21 (14.30; 20.43)	15.75 (10.90; 20.20)	18.94 ±8.74 (15.58; 22.21)	17.10 (12.60; 27.50)	1.57 ±6.90 (–1.00; 4.15)	0.65 (–2.50; 3.30)	0.434	0.608
HOMA–IR	3.64 ±1.77 (2.99; 4.29)	3.32 (2.02; 4.90)	4.15 ±2.29 (3.30; 4.99)	3.83 (2.41; 5.04)	0.50 ±1.41 (–0.01; 1.02)	0.51 (–0.34; 1.03)	0.041	4.20 ±2.52 (3.26; 5.14)	3.56 (2.42; 4.49)	4.44 ±2.36 (3.55; 5.32)	3.82 (2.78; 5.67)	0.24 ±1.62 (–0.37; 0.84)	0.36 (–1.02; 0.79)	0.837	0.260
TC mg/dl	221.61 ±40.63 (206.71; 236.52)	222.00 (193.00; 257.00)	213.12 ±37.88 (199.23; 227.03)	213.00 (180.00; 238.00)	–8.48 ±31.95 (–20.20; 3.24)	–3.00 (–22.00; 18.00)	0.355	216.30 ±43.90 (199.91; 232.69)	225.00 (183.00; 249.00)	215.6 ±35.73 (202.26; 228.94)	219.50 (186.00; 237.00)	–0.70 ±24.58 (–9.880; 8.48)	2.50 (–16.00; 19.00)	0.821	0.419
HDL–C mg/dl	47.81 ±11.00 (43.77; 51.84)	48.00 (39.00; 56.00)	47.74 ±11.42 (43.55; 51.93)	47.00 (41.00; 54.00)	–0.06 ±5.40 (–2.04; 1.92)	–3.00 (–22.00; 18.00)	1.000	50.87 ±10.05 (47.11; 54.62)	50.50 (44.00; 57.00)	50.47 ±9.65 (476.86 54.07)	52.00 (44.00; 55.00)	–0.41 ±5.44 (–2.48; 1.66)	–1.00 (–3.00; 2.00)	0.421	0.629
LDL–C mg/dl	142.19 ±38.93 (127.91; 156.47)	136.00 (114.00; 173.00)	135.65 ±33.95 (123.19; 148.10)	137.00 (104.00; 157.00)	–6.55 ±31.14 (–17.97; 4.87)	–3.00 (–17.00; 17.00)	0.5501	139.30 ±38.25 (125.02; 153.58)	142.00 (110.00; 162.00)	137.60 ±32.44 (125.49; 149.71)	133.50 (110.00; 162.00)	–1.70 ±17.85 (–8.36; 4.97)	–0.50 (–10.00; 13.00)	0.991	0.773
TG mg/dl	143.35 ±55.6 (122.95; 163.76)	127.00 (104.00; 175.00)	138.64 ±62.11 115.86; 161.43)	125.00 (97.00; 184.00)	–4.71 ±31.29 (–16.19; 6.77)	–9.00 (–23.00; 10.00)	0.304	137.60 ±62.51 (114.26; 160.94)	120.00 (102.00; 170.00)	140.23 ±81.88 (109.66; 170.81)	108.00 (88.00; 164.00)	2.63 ±40.69 (–12.56; 17.83)	–7.00 (–28.00; 30.00)	0.959	0.564
Adiponectin µg/ml	7.57 ±3.65 (6.23; 8.91)	7.57 (4.49; 10.44)	7.76 ±5.41 (5.77; 9.74)	6.69 (3.71; 10.74)	–0.19 ±4.84 (–1.59; 1.96)	–0.39 (–1.24; 0.53)	0.100	7.35 ±4.33 (5.73; 8.97)	6.70 (5.09; 8.31)	7.56 ±4.32 (5.95; 9.18)	6.98 (4.43; 9.98)	0.21 ±1.68 (–0.42; 0.83)	0.25 (–0.70; 1.21)	0.459	0.094

Table 3 – cont.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Apelin ng/l	93.67 ±64.40 (70.05; 117.30)	68.19 (38.78; 153.19)	91.77 ±65.03 (67.92; 115.63)	67.99 (41.24; 142.71)	–1.90 ±24.8 (–10.99; 7.20)	0.11 (–11.01; 6.75)	0.769	87.88 ±68.08 (62.46; 113.30)	51.49 (38.37; 120.96)	89.34 ±68.59 (63.73; 114.94)	47.82 (36.24; 123.93)	1.45 ±22.62 (–6.99; 9.90)	–1.53 (–8.54; 9.73)	0.837	0.960
Ghrelin ng/ml	12.70± 4.20 (11.15; 14.24)	12.01 (10.26; 13.64)	14.80 ±6.39 (12.46; 17.15)	15.28 (12.06; 19.37)	2.10 ±5.84 (–0.04; 4.25)	2.48 (–1.58; 6.14)	0.043	11.32 ±6.63 (8.84; 13.79)	9.34 (7.16; 13.64)	12.50 ±5.56 (10.43; 14.58)	12.22 (9.91; 13.70)	1.18 ±6.69 (–1.31; 3.68)	1.83 (–1.69; 4.67)	0.088	0.762
Leptin ng/ml	22.96 ±12.38 (18.41; 27.50)	20.81 (14.13; 28.59)	21.46 ±12.38 (16.92; 26)	18.48 (12.36; 28.28)	–1.50 ±4.23 (–3.05; 0.05)	–2.03 (–3.49; 0.48)	0.034	22.66 ±10.99 (18.56; 26.77)	19.38 (14.18; 28.35)	22.50 ±11.73 (18.12; 26.88)	17.66 (15.20; 26.49)	–0.16 ±6.31 (–2.52; 2.19)	–0.58 (–2.62; 3.20)	0.797	0.237
Leptin/ adiponectin	3.81 ±2.30 (2.97; 4.65)	3.32 (1.97; 5.26)	4.41 ±4.87 (2.62; 6.19)	3.01 (1.85; 4.86)	3.56 ±14.28 (–1.68; 8.80)	0.93 (–2.93; 5.29)	0.829	3.95 ±2.58 (2.98; 4.91)	3.25 (2.37; 5.42)	4.06 ±3.50 (2.75; 5.37)	2.62 (1.87; 5.60)	5.09 ±34.41 (–7.76; 17.94)	–0.43 (–3.17; 3.01)	0.371	0.302
Omentin ng/ml	287.51 ±86.06 (256.24; 319.37)	282.40 (248.00; 326.56)	274.42 ±86.12 (242.83; 306.01)	272.80 (208.12; 320.32)	–13.38 ±73.3 (–40.27; 13.50)	–4.68 (–84.64; 48.40)	0.337	263.87 ±100.61 (226.31; 301.44)	259.70 (180.72; 316.12)	283.33 ±95.36 (247.72; 318.94)	270.10 (216.76; 368.68)	19.46 ±75.37 (–8.68; 47.60)	23.38 (–7.52; 88.96)	0.088	0.056
Resistin ng/ml	8.33 ±4.17 (6.80; 9.86)	6.86 (4.78; 10.74)	9.03 ±4.38 (7.42; 10.63)	8.72 (5.22; 11.90)	0.70 ±2.46 (–0.20; 1.60)	0.86 (–1.68; 2.24)	0.158	7.46 ±3.56 (6.13; 8.79)	6.37 (4.94; 8.72)	8.00 ±2.99 (6.89; 9.12)	7.78 (6.04; 10.12)	0.54 ±2.55 (–0.41; 1.49)	0.41 (–0.84; 1.94)	0.254	0.778
Visfatin ng/ml	9.51 ±6.43 (7.15; 11.87)	8.24 (6.55; 9.79)	9.56 ±5.42 (7.57; 11.54)	8.96 (7.22; 10.10)	0.05 ±2.42 (–0.84; 0.94)	0.43 (–1.56; 1.76)	0.440	9.17 ±3.36 (7.91; 10.42)	8.56 (7.09; 10.24)	8.53 ±2.65 (7.54; 9.53)	8.32 (7.08; 9.47)	–0.63 ±1.77 (–1.29; 0.03)	–0.39 (–1.91; 0.77)	0.090	0.046

[1]Within-group effect.
[2]Between-group effect (p for Δ).
CLA – conjugated linoleic acid, HDL-C – high-density lipoprotein cholesterol, HOMA-IR – homeostatic model assessment of insulin resistance, IQR – interquartile range, LDL-C – low-density lipoprotein cholesterol, SD – standard deviation, TC – total cholesterol, TG – triglycerides, 95% CI – 95% confidence interval.

DISCUSSION

After twelve weeks of CLA supplementation, HOMA-IR and ghrelin levels were significantly increased, while leptin concentrations were reduced (within-group effect). However, no differences were observed between the intervention and control groups in glucose, insulin, and lipid parameters. Moreover, CLA supplementation exerted a contrasting effect on visfatin levels compared to the control group (between-group effect).

Previous studies have indicated potential antidiabetic effects of CLA, possibly through the activation of peroxisome proliferator-activated receptor gamma (PPAR-γ), which facilitates glucose uptake and insulin secretion (Houseknecht et al., 1998). For instance, Gaullier et al. (2007) reported a reduction in glucose and glycated haemoglobin levels after six months of CLA supplementation, although similar effects were observed in the placebo group. The CLA capsules used in their study contained 37.5% cis-9, trans-11, and 38% trans-10, cis-12, and the remainder consisted of other fatty acids, with participants consuming 3.4 g CLA per day.

The positive impact of CLA supplementation on glucose homeostasis was also highlighted by Ebrahimi-Mameghani et al. (2016), who found similar effects in obese individuals with non-alcoholic fatty liver disease. Additionally, a meta-analysis by Liang et al. (2023) revealed that CLA supplementation combined with a training program was more effective than exercise alone in reducing insulin resistance. Colakoglu et al. (2006) further demonstrated the beneficial effect of six weeks of CLA supplementation alongside exercise on glucose homeostasis in young women.

However, these findings contrast with our results, which showed no effect of CLA supplementation on glucose and insulin homeostasis. Similarly, a recent meta-analysis by Rahbar et al. (2017) concluded that cis-9, trans-11, and trans-10, cis-12 CLA, when administered as a supplement or used to enrich foods, did not affect fasting glucose levels.

Furthermore, Gaullier et al. (2004) investigated the 12-month effects of 4.5 g olive oil (placebo), 4.5 g 80% CLA-free fatty acids, and 4.5 g 76% CLA-triacylglycerol in a cohort of 180 healthy overweight men and women. Their findings indicated no significant change in fasting glucose concentrations following the intervention period. Although glycated haemoglobin increased in all groups, there were no differences between the supplements. Raff et al. (2009) also examined the impact of 5.5 g/d of cis-9, trans-11, trans-10, cis-12 CLA and cis-9, trans-11 CLA in healthy postmenopausal women. Their study revealed no significant differences in the impact of the three supplements on fasting serum insulin and glucose concentrations, or HOMA-IR, following the 16-week intervention. However, in a post-hoc analysis, the women were divided into terciles based on their waist circumference. This revealed that women in the CLA-mix group with the largest waist circumferences had significantly higher serum insulin concentrations.

Other studies have reported a negative effect of CLA supplementation on glucose homeostasis. For example, Risérus et al. (2002) studied the effects of 3.4 g/day of the trans-10, cis-12 CLA isomer versus placebo in obese men. While the CLA mixture had no effect on glucose metabolism, the trans-10, cis-12 CLA isomer significantly increased insulin resistance after 12 weeks. Moloney et al. (2004) also investigated CLA supplementation in individuals with type 2 diabetes mellitus, finding that it significantly raised fasting glucose concentrations and reduced insulin sensitivity after eight weeks.

Moreover, a recent meta-analysis by Ghodoosi et al. (2023) suggested that while CLA supplementation may elevate fasting glucose levels, it does not significantly affect insulin resistance or glycated haemoglobin. The mechanism by which CLA might negatively impact glucose and insulin metabolism remains unclear.

Here, we report that CLA supplementation had no impact on the lipid profile, aligning with most, though not all, previous findings. A recent meta-analysis of 56 randomised controlled trials found that CLA supplementation significantly improved HDL-C concentrations but increased TC, LDL-C, and TG levels (Asbaghi et al., 2022). Conversely, another meta-analysis demonstrated that consuming CLA-enriched foods or supplements had favourable effects on LDL-C levels (Derakhshande-Rishehri et al., 2015). The authors proposed that CLA supplementation might reduce LDL-C levels by inhibiting apolipoprotein B secretion or enhancing the clearance rate of circulating LDL-C via increased LDL receptor activity (Grundy

and Denke, 1990; Storkson et al., 2005). Additionally, dietary CLA may promote faecal excretion of total neutral sterols (Thomas Yeung et al., 2000) and inhibit cholesterol absorption by downregulating intestinal acyl-coenzyme A cholesterol acyltransferase (Aminot-Gilchrist and Anderson, 2004).

A positive effect of CLA consumption on the lipid profile was also reported by Ebrahimi-Mameghani et al. (2016) in obese subjects with non-alcoholic fatty liver disease. Similarly, Jenkins et al. (2014) found that six weeks of supplementation with cis-9, trans-11 and cis-10, trans-12 CLA isomers combined with aerobic training effectively decreased TG levels in untrained to moderately trained men.

In contrast, Iwata et al. (2007) observed no effect of 5.4 g CLA-triacylglycerol (3.4 g as CLA) or 10.8 g CLA-triacylglycerol (6.8 g as CLA), compared to placebo (10.8 g safflower oil), on the lipid profile of healthy, overweight men after 12 weeks of intervention. The CLA-triacylglycerol in this study contained equal proportions of cis-9, trans-11, and trans-10, cis-12 isomers. Similarly, Ribeiro et al. (2016) reported no improvement in the lipid profile of young adult obese women who received CLA supplementation alongside aerobic exercise.

Tavakkoli Darestani et al. (2010) also found no effect of 12 weeks of CLA intervention (3.2 g CLA of 50:50 cis-9, trans-11 and trans-10, cis-12 isomers) on TC, LDL-C, HDL-C, or TG levels in postmenopausal women. Furthermore, Pfeuffer et al. (2011) reported no impact of an isomeric mixture of CLA on the lipid profile of healthy individuals with excessive body weight, while Wanders et al. (2010) observed that a high content of cis-9, trans-11 and trans-10, cis-12 CLA might adversely affect the TC to HDL-C ratio in healthy individuals.

Visfatin is an adipokine released from various sources, including visceral fat and macrophages. It has been shown that visfatin may affect glucose metabolism and increase inflammation (Abdalla, 2022). Previous studies reported higher visfatin concentrations in obese women than in healthy subjects (Zahorska-Markiewicz et al., 2007) and noted that visfatin levels might decrease after weight loss (Haider et al., 2006).

Our randomised controlled trial is the first to assess the effect of CLA intervention on visfatin concentrations. The present study observed opposing effects on visfatin levels in the intervention and control groups (between-group comparisons, median (IQR): 0.43 (–1.56; 1.76) vs.–0.39 (–1.91; 0.77) ng/ml, $p = 0.046$). However, this result appears to be due to random chance.

We reported that leptin concentrations significantly decreased in the CLA group after the intervention. However, no differences were found between the effects of CLA and placebo supplementation on adiponectin, apelin, ghrelin, leptin, the leptin-to-adiponectin ratio, omentin, and resistin levels. Medina et al. (2000) also assessed the effect of CLA supplementation (3 g/day) on healthy women. They observed a significant decrease in plasma leptin concentrations, adjusted for adiposity, during the first seven weeks in the CLA-treated group. However, these levels returned to baseline during the final two weeks of the study. After 57 days of supplementation, mean leptin levels in the CLA-treated group were not significantly different from those in the placebo-treated group.

In contrast, Syvertsen et al. (2007) found no significant differences in leptin levels, either within or between groups of overweight and obese participants, after six months of supplementation with either 3 × 4 g/d CLA or placebo. Similarly, Joseph et al. (2011) observed no significant change in circulating adiponectin levels from baseline to endpoint following CLA supplementation, compared with the control treatment in hyperlipidemic men. However, MacRedmond et al. (2010) reported that in overweight mild asthmatic subjects, significant reductions in weight and BMI in the CLA group were associated with a decrease in the leptin/adiponectin ratio after 12 weeks of supplementation.

Sneddon et al. (2008) found that supplementation with a combination of cis-9, trans-11, and trans-10, cis-12 CLA isomers and a mixture of n-3 polyunsaturated fatty acids led to increased adiponectin levels in younger obese individuals. Maher et al. (2021) examined the effect of breakfast consumption containing either 23.06 g vegetable oil, 25 g medium-chain triglycerides oil, or 6.25 g CLA with 16.80 g vegetable oil. They reported no significant difference in ghrelin levels between the CLA and other groups. In their meta-analysis, Ghodoosi et al. (2023) concluded that CLA supplementation decreased leptin levels but did not affect adiponectin concentrations. Another

meta-analysis by Haghighatdoost and Hariri (2018) suggested that CLA may reduce leptin levels, but only in studies involving overweight male subjects with a duration of less than eight weeks.

Several factors could explain the differences between our results and previous findings. First, the effect of CLA supplementation may vary between men and women, as well as among individuals with optimal body weight, excess weight, or obesity. Additionally, the duration of the intervention period can influence the outcomes. For instance, Rastgoo et al. (2023) found that CLA supplementation reduced adiponectin and leptin levels only in women. In a recent meta-analysis, Haghighatdoost and Hariri (2018) reported that, compared to the control group, CLA administration significantly reduced serum leptin levels in men or overweight individuals, particularly in studies with an intervention duration of less than eight weeks. Furthermore, Mohammadi-Sartang et al. (2018) showed that CLA supplementation significantly reduced leptin levels exclusively in obese individuals and in studies with a duration of less than 24 weeks.

The dose of CLA can also influence study outcomes. Previous studies have shown that a high dose of CLA (6.4 g/d) for 12 weeks increased levels of C-reactive protein and interleukine-2, while a lower dose (3 g/d) had no effect on the inflammatory markers (Steck et al., 2007). Berven et al. (2000) assessed the safety of 3.4 g CLA or 4.5 g olive oil daily for 12 weeks and found adverse events in 10% of participants. However, there were no significant differences in the number of adverse events, blood safety parameters, or vital signs between the groups. Iwata et al. (2007) also examined the safety of CLA supplementation in a study involving healthy participants. While more adverse events occurred in the CLA groups than in the placebo group, all cases were of mild to moderate intensity. Serum aspartate aminotransferase (AST) levels did not differ significantly between the groups; however, serum alanine aminotransferase (ALT) concentrations were higher in the group receiving 10.8 g CLA-triacylglycerol compared to the placebo group. Notably, at a dose of 3.4 g/day, CLA supplementation was found to be safe, with no significant changes in vital signs. In contrast, a recent meta-analysis by Mirzaii et al. (2016) suggested that CLA intake might increase AST levels, but does not affect ALT concentrations. In our previous study, however, we found no difference in the effects of CLA compared to placebo on liver enzymes (Mądry et al., 2020). Similarly, a meta-analysis by Haghighat et al. (2022) reported no effect of CLA supplementation on liver function.

Different CLA isomers may have opposite effects on the parameters analysed. Venkatramanan et al. (2010) investigated the impact of milk enriched with either natural or synthetic CLA isomers and found no effect on the lipid profile compared to the control group. In contrast, Tricon et al. (2004) observed differing effects of cis-9, trans-11 and trans-10, cis-12 CLA on blood lipids in healthy humans. Specifically, trans-10, cis-12 CLA increased the LDL-C:HDL-C and TC:HDL-C ratios, while cis-9, trans-11 CLA reduced them. These opposing effects suggest that the impact of these two isomers could cancel each other out, potentially resulting in no significant differences between the CLA and control groups. In fact, several studies using a mixture of cis-9, trans-11 and trans-10, cis-12 isomers, observed no effect of CLA supplementation (Rahbar et al., 2017; Tavakkoli Darestani et al., 2010). Variations in study outcomes may also stem from differences in the proportions of isomers used. For instance, Noone et al. (2002) randomly assigned participants to receive 3 g per day of either a 50:50 or 80:20 blend of cis-9, trans-11 and trans-10, cis-12 CLA, or linoleic acid (control) for eight weeks. The 50:50 CLA blend significantly reduced TG concentrations, whereas the 80:20 blend significantly reduced very low-density lipoprotein cholesterol concentrations.

Moreover, the effectiveness of the intervention may be influenced by reductions in body weight and improvements in body composition. However, as previously documented, CLA supplementation significantly reduced total body fat, as well as android, gynoid and visceral adipose tissue. Additionally, it significantly increased lean body mass relative to height compared to the placebo group (Mądry et al., 2020). Furthermore, CLA supplementation led to a significant reduction in hip circumference compared to the placebo, although it did not affect body weight, BMI or waist circumference (Madry et al., 2016). However, we observed no significant differences in the effects of CLA intervention on glucose, insulin, or lipid metabolism.

The type of placebo used may also have influenced the findings. Most studies use olive oil as a placebo (Gaullier et al., 2004; Raff et al., 2009), which could significantly affect conclusions due to its favourable fatty acid composition (Špika et al., 2021). In our study, the placebo group received sunflower oil, as was the case in several other trials (Benito et al., 2001; Chang et al., 2020; Desroches et al., 2005). It has been suggested that linoleic acid in placebo oils can be biohydrogenated by gastrointestinal bacteria into CLA. Specifically, non-ruminal bacteria inhabiting the human gastrointestinal tract, such as *Lactobacillus* and *Bifidobacterium,* may convert linoleic acid to CLA, probably through an intermediate like vaccenic acid (Devillard et al., 2007). We selected sunflower oil as a placebo because it is part of the typical diet and has organoleptic properties and an energy value similar to those of CLA.

Our study has several limitations, including the relatively short duration period. Additionally, we did not measure CLA levels in the blood or assess CLA intake through diet. Furthermore, these findings are only applicable to overweight or obese women, so they may not be generalisable to other populations.

Nonetheless, this well-designed randomised controlled trial, conducted in accordance with the CONSORT guidelines, aimed to evaluate the effectiveness of CLA supplementation on cardio-metabolic parameters in women with excessive body weight. Notably, this is one of the first trials to report the effects of CLA supplementation on apelin, resistin, and omentin levels in humans.

In conclusion, our results do not support the health-promoting effects of CLA on glucose and lipid metabolism in overweight and obese women. However, further, larger-scale studies are needed to better understand the impact of CLA supplementation on adipokine levels.

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During the course of this study, K.M. was a Ph.D. student in the Department of Pediatric Gastroenterology and Metabolic Diseases, Poznan University of Medical Sciences.

DECLARATIONS

Data statement

The data presented in this study are available on request from the corresponding author (J.W.).

Ethical Approval

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Bioethics Committee of the Poznan University of Medical Sciences in Poland (protocol code: 606/12, 453/13, 358/14, 398/15).

Competing Interests

The authors declare that they have no conflicts of interest.

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