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Effect of Conjugated Linoleic Acid on Leptin Level: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Key words
adipokine, fatty acid, randomization, adipose tissue

received 04.07.2017
accepted 21.12.2017

Bibliography
DOI https://doi.org/10.1055/s-0044-100041
Horm Metab Res 2018; 50: 106–116

ISSN 0018-5043

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ABSTRACT

The results of human clinical trials examining the effects of conjugated linoleic acid (CLA) on leptin concentration are inconsistent. Our objective was to elucidate the role of conjugated linoleic acid supplementation on leptin through a systematic review and a meta-analysis of available randomized placebo-controlled trials (RCTs). We searched the PubMed, SCOPUS, and ISI web of science up to February2017, in English, to identify RCTs investigating the effect of CLA supplements on plasma leptin concentrations. Weighted mean differences (WMDs) and their respective 95 % confidence intervals (CIs) were calculated to assess the efficacy of CLA on leptin concentration by using random effects. Statistical heterogeneity, study quality, meta-regression and publication bias were used based on standard methods. Nineteen RCTs (comprising 26 treatment arms) with 1045 subjects were included in this meta-analysis. Random-effect meta-analysis found a slight but not significant reduction in plasma leptin concentrations (WMD: −0.38 ng/ml, 95 % CI: −1.08, 0.32, p = 0.286); I^2 = 53.24 %, p = 0.001), following CLA supplementation. The pooled effect size was robust and remained non-significant in the leave-one-out sensitivity analysis. Subgroup analysis based on BMI status showed that the CLA supplementation significantly reduces leptin when used for obese subjects (WMD: −1.47 ng/ml, 95 % CI: −2.15, −0.79, p < 0.001) and in the subset of trials lasting < 24 weeks of duration (WMD: −0.76 ng/ml, 95 % CI: −1.40, −0.12, p = 0.019). CLA supplementation might moderately decrease circulatory leptin levels only among obese adults for shorter than 24 weeks. Additional high-quality studies are needed to replicate our results.

Introduction

Conjugated linoleic acid (CLA), as a lipid derived from fatty tissues in animals [1], is a group of polyunsaturated fatty acids [2]. It can be found in foods from ruminant sources such as meat and dairy products. They are formed naturally through the process of bacterial bio-hydrogenation in the intestine of ruminants [3]. However, they are found just in milligram quantities in foods [4]. Hence, its supplementary types are present commercially due to its possible beneficial properties considering its effects on obesity and body composition [5]. Moreover, CLA bear various biological features including its effects on carcinogenesis [6], atherosclerosis [7], and immune-modulation [8]. Other properties of CLA might be pertinent to its protecting effects against diabetes and hypertension [9–13]. CLA might possess weight-management properties via decreasing energy, food intake, and lipogenesis, and increasing lipolysis, energy expenditure, and fat oxidation [14–16]. Obesity and changes in body composition by increasing body fat is associated with changes in adipocytokines, especially leptin [17]. All of the mentioned effects of CLA in weight-management might be through regulating adipocyte gene expression [9, 15, 18]. Recent studies focused on the effects of CLA on body composition, especially body fat and its mechanisms [19]. The mechanism of the effects of CLA

on body composition is unknown [5]. However, effects of CLA on body composition might be due to reduction of body fat through leptin. Leptin, as a product of ob gene, can modulate adiposity and body fat by decreasing food intake and increasing metabolic rate [20, 21]. CLA effects on body composition might be through increasing circulating leptin [22]. On the other hand, insulin might regulate or increase the production of leptin by adipose tissue [23, 24]. As CLA can affect insulin concentration and sensitivity [5], its effect on leptin concentration is unknown. In addition to adipose tissue, insulin is the second major factor for the changes in circulating leptin [25]. As insulin concentration might be affected by CLA consumption and this can in turn affect circulating leptin [5], effect of CLA consumption on circulating leptin is unknown and needs more investigation.

In some studies, decreasing effects of CLA supplementation on circulating leptin was reported [22, 26], while in some other studies, no effect was reported [2, 27]. The discrepancies among studies might be due to various methodologies or designs of trials, durations, doses, quality of trials, type of supplementation, and so on. Therefore, it would not be easy to draw a conclusion out of RCTs about the efficacy of CLA supplementation on leptin concentration.

To the best of our knowledge, no systematic review and meta-analysis were done to assess the effect of CLA supplementation on leptin concentration. So, due to the conflicting results in this regard, we conducted a systematic review to summarize the data from various RCTs, and for quantifying the effect of CLA supplementation on circulating leptin, we also performed a meta-analysis to have a better conclusion.

Materials and Methods

Search strategy

Our meta-analysis was designed based on the guidelines of the PRISMA statement [28]. SCOPUS (http://www.scopus.com), Medline (http://www.ncbi.nlm.nih.gov/pubmed), and ISI web of sciences database were searched up to February 2017 investigating the influence of CLA supplementation on leptin concentrations using the following MeSH terms and related key words: (((((“trans-10,cis-12-conjugated linoleic acid” [Supplementary Concept]) OR “cis-9, trans-11-conjugated linoleic acid” [Supplementary Concept]) OR “conjugated linoleic acid” [Title/Abstract]) OR CLA[Title/Abstract])) AND (((“Adipokines”[Mesh]) OR adipocytokines [Title/Abstract]) OR “Leptin”[Mesh]). Moreover, we handsearched the reference list of included articles and also related reviews and meta-analysis.

Study selection

Two independent investigators (M.A and S.E) reviewed titles and abstracts of all identified studies to ascertain whether these studies are eligible for our meta-analysis based on inclusion criteria. In case of discrepancies, the third investigator (M.M) was involved: (i) being an RCTs with either parallel or crossover design in adults (age ≥ 18 years old); (ii) having an intervention duration of at least 2 weeks; (iii) having a suitable controlled design, that is, if CLA was supplemented as an adjunct to another drug/supplement, the control group contained that drug/supplement; and (4) presenting sufficient data on leptin concentrations and their corresponding standard deviations (SDs) at baseline and at the end of follow-up in CLA and control group. Exclusion criteria were: (i) non-RCTs, (ii) study had lack of a suitable control group in the study design, (iii) duplicate publication from the same study, and (iv) study had lack of adequate information on baseline or follow-up leptin concentrations.

Data extraction

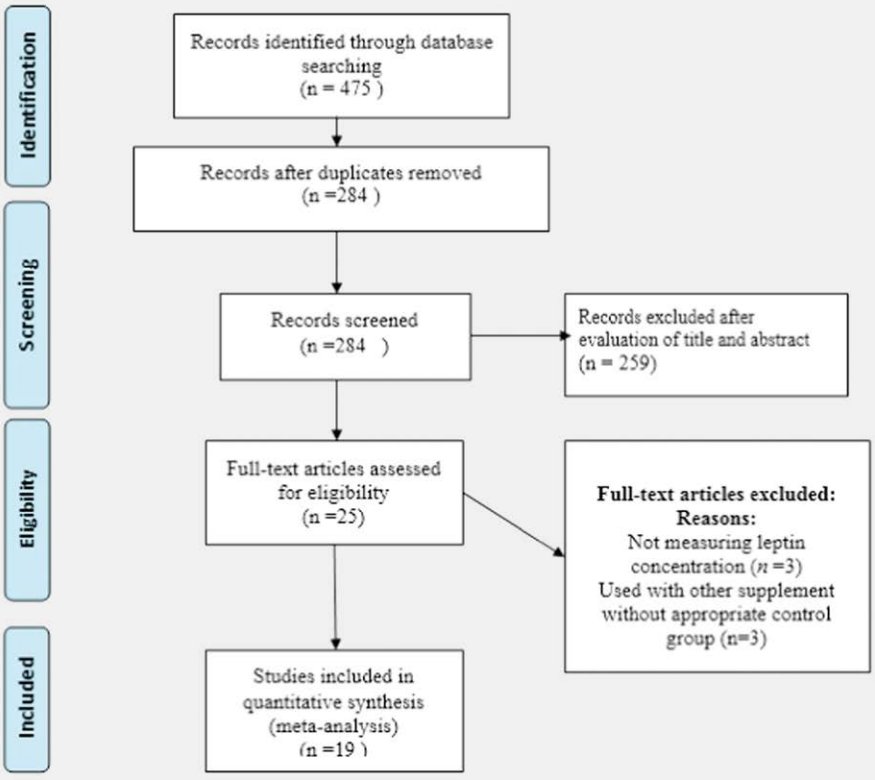
We used inclusion-exclusion screening form to select eligible articles. After selecting the eligible articles, the data of RCTs were reviewed independently by two authors (Y.J and S.E) and the following data were abstracted using a standardized electronic form: first author’s name, publication year, study location, study design, duration of the intervention, sample size in each group, form and administered dose of CLA, type of placebo, age, body mass index (BMI), and % women. We also extracted the mean values, and SDs of our interested outcome at baseline, post-intervention, and/or change between baseline and post-intervention. For studies that reported data at multiple measurements or multiple doses, only the measures of the longest duration of treatment at the end of trials and also each dose of supplementation were used in the meta-analysis.

Quality assessment

The quality of eligible studies was evaluated using the quantitative 5-point Jadad scale [29]. Articles were assigned 0 or 1 point for each of the following 5 criteria: 1) randomization, 2) suitable method of randomization, 3) double-blinding, 4) suitable method of double-blinding, and 5) explanation and reason of withdrawals and dropouts [29]. Articles with scores with ≥ 3 and ≤ 2 were considered high and low quality, respectively [30].

Quantitative data synthesis and statistical analysis

The mean leptin changes from baseline were used to assess the effect of CLA in both of the intervention and placebo groups. Net changes were calculated as follows: value at the end of the trial minus the value at baseline. Effect sizes were defined as weighted mean difference (WMD) and 95 % confidence interval (CI). In the event of no reported SD of the mean difference, it was calculated as follows: SDs = square root [(SD pre-intervention)2 + (SD post-intervention)2 – (2 R × SD pre- intervention × SD post-intervention)], assuming a correlation coefficient of 0.5, because this value for R is a conservative estimate between 0 and 1 [31]. When SE was reported in place of SD, we converted it to SD for analyses: $SD = SE \times \sqrt{n}$, where n is the number of participants in each group. Plot digitizer software was used to extract data when the outcome variable was presented in graphic form only. Statistical heterogeneity between studies was evaluated using Cochran’s Q-test (significance set at $p < 0.1$) and I2 (≥ 50 % assumed to indicate substantial heterogeneity among studies). In the presence of heterogeneity, pooled effect size was calculated using a random effects model; otherwise, we applied a fixed-effects model. Sensitivity analysis was used to explore the extent to which inferences might depend on a particular study using the leave-one-out method (i. e., removing a single trial at a time and repeating the analyses). Meta-regression was performed using unrestricted maximum likelihood meth-



▶ **Fig. 1** Flow diagram of the study selection procedure showing the number of eligible randomized controlled trials for the meta-analysis of the effect of CLA supplementation on plasma leptin concentrations.

od to explore the association between the net effect size, CLA dose, duration of supplementation, and baseline BMI of subjects. Publication bias was assessed by funnel plot, Begg's rank correlation, and Egger's weighted regression tests. In the event of publication bias, the Duval and Tweedie 'trim and fill' and 'fail-safe N' methods were utilized [32]. The meta-analysis was performed by STATA software (Biostat, NJ, USA) [33]. A p-value < 0.05 was considered statistically significant.

Results

Search results and study selection

The detailed process of the study selection is shown in ▶ **Fig. 1**. In total, 475 articles (106 from PubMed, 168 from Scopus, 201 from ISI web of sciences) were initially identified, and 188 articles were excluded, either because of duplication (n = 191) or because they were deemed irrelevant to this meta-analysis after careful screening of the titles and abstracts. Therefore, 25 potentially relevant articles were selected for full text evaluation. After the careful evaluation, six articles were excluded for several reasons: three articles were excluded because they did not contain data on leptin concentrations and three studies were excluded because CLA was given as a part of a multicomponent supplement. Thus, 19 RCTS with 26 treatment arms were ultimately selected for inclusion in the meta-analysis [34–50].

Study characteristics

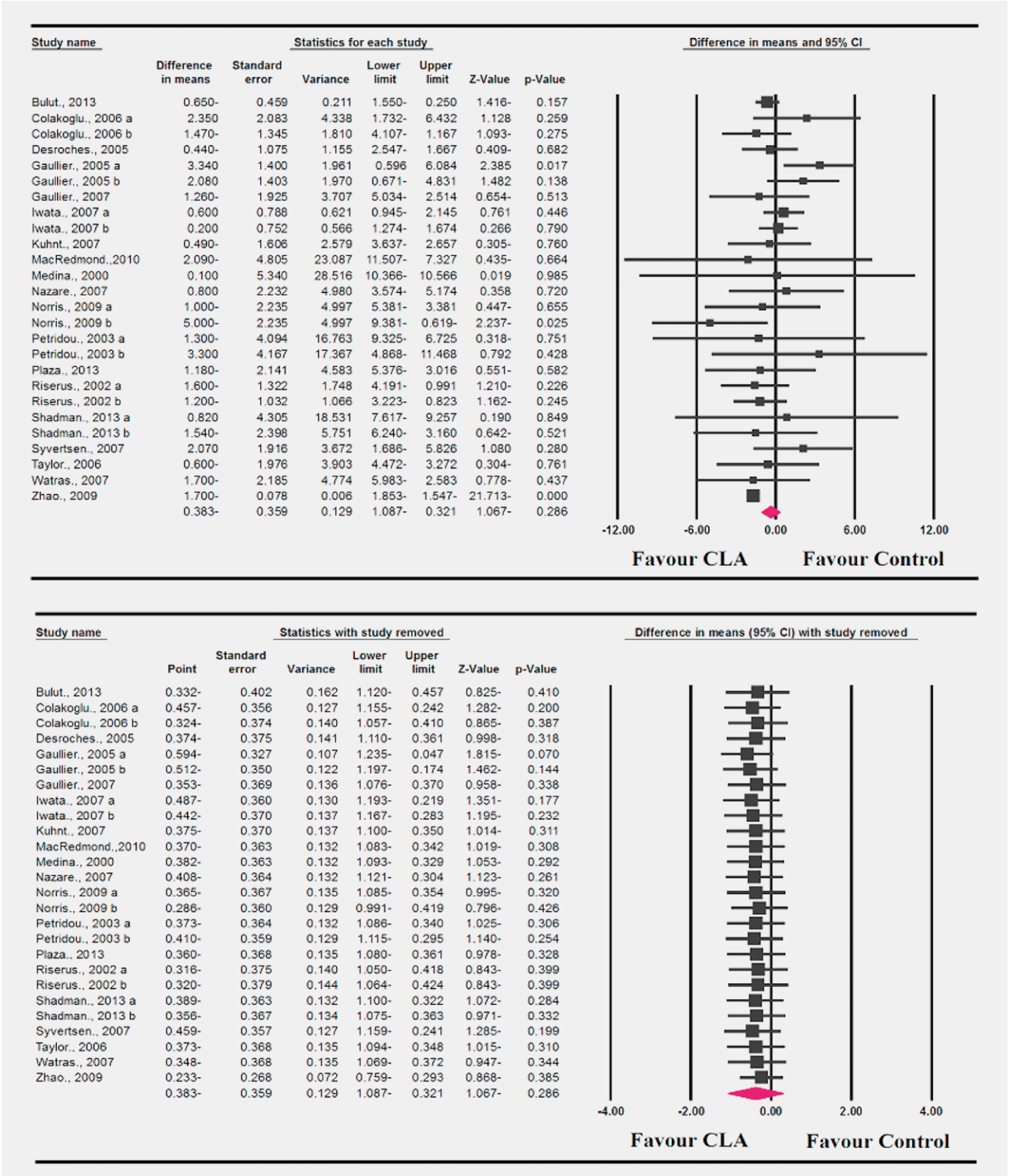
Nineteen published studies with a total of 1045 participants, including 556 subjects in the CLA group and 489 patients in the control group, were identified in this meta-analysis. A summary of the study characteristics included in the meta-analysis is presented in ▶ **Table 1**. The number of participants in these trials ranged from 16 to 120 subjects. The studies included were published between 2000 and 2013, and were conducted in Spain [47], Norway [36, 45], Germany [37, 41], Canada [35, 38], USA [22, 50], France [40], Sweden [43], Iran [44], Japan [48], England [49], Turkey [34], Greece [42], and China [46]. CLA dosing ranged from 2.1 to 8 g/d and the duration of CLA intervention varied from 6 to 48 weeks. Of the 17 trials used in the meta-analysis, four trials were conducted exclusively in women [22, 34, 41, 42], four trials were conducted in men [35, 43, 48, 49] and nine trials were conducted in both sexes [36–38, 40, 44–47, 50]. Seven trials selected healthy overweight and obese subjects [35, 36, 45, 47–50]; of the remaining 10 trials, five studies were conducted in healthy subjects [34, 37, 39, 40, 42], two were performed in type 2 diabetes patients [41, 44], one in overweight mild asthmatics [38], one in obese metabolic syndrome [43], and one in obese individuals with stage 1 uncontrolled essential hypertension [46]. Study design of almost all included studies was parallel-group, except for one that was cross-over. One trial had three arms comparing CLA + vitamin E, CLA + vitamin E placebo, CLA placebo + vitamin E placebo. Demographic and baseline parameters of the included studies are shown in ▶ **Table 1**.

▶ **Table 1** Demographic characteristics and baseline parameters of the included studies.

Author, and publication year	Location	Sample size and population	Mean age	BMI	CLA dose and form (g/d)	Isomers	Placebo dose and form	Duration	Design	Jadad score
Bulut, 2013	Turkey	Eighteen healthy sedentary slightly overweight (BMI between 26.47 and 26.83) male subjects	19–31	29.45	3 g/d, CLA-mix	(50:50) c9, t11 *t*10, *c*12	3 g inulin (Raftiline) powder	4	DB, R, PC	3
Colakoglu, 2006	Turkey	Forty-four females, healthy exercising normal-weight	21.5	28.4	3·6 g/d, CLA-mix	*c*9, t11–*t*10, *c*12	Control	12	SB, R, PC	3
Desroches, 2005	Canada	16 overweight and obese men	36.6	31.2	4.22 g CLA/100 g butter fat)	0.38 g CLA/100 g butter fat	0.38 g CLA/100 g fatty acids	4	RP	3
Gaullier, 2005	Norway	134 male and female, healthy overweight	46.26	28.2	3.4 g/d CLA-TG 3.4 g/d CLA-FFA	(50:50) *c*9, *t*11 *t*10, *c*12 (50:50) *c*9, *t*11/*t*10, *c*12	3.4 g/d placebo	48	RC	4
Gaullier, 2007	Norway	118 males and females, healthy overweight and obese	47.25	35	3·4 g/d, CLA-TAG	*c*9, *t*11–*t* 10, *c*12 (37·5:38·0)	4·5 g/d, olive oil	24	DB, R, PC, Parallel	4
Iwata, 2007	Japan	60 male, healthy overweight and obese	25–60	25–35	3.4 g/d CLA-TG 6.8 g/d CLA-TG	(50:50) *c*9, *t*11/*t*10, *c*12	10.8 g/d high-linoleic safflower oil	12	DB, R, PC, Parallel	3
Kuhnt, 2007	Germany	24 male and female, healthy	58.2	27.9	6 g/d, CLA-mix	*trans*-11- and *trans*-12–18:1, 60 %; *cis*-11- and *cis*-12–18:1, 20 %; 18:0, 11 %	543	12	R, PC	3
MacRedmond, 2011	Canada	26 adult subjects with mild asthma	31	27.5	4.5 g/d, CLA-mix	(36.4:37) c9, t11/*t*10, *c*12	4.5 g olive oil	12	DB, R, PC	3
Medina, 2000	USA	17 women , healthy	56.8	27.4	3 g/d, CLA-mix	22.6 % *t*-10, *c*-12; 23.6 % *c*-11, *t*-13; 17.6 % *c*-9, *c*-11; 16.6 % *t*-8, *c*-10; 7.7 % *t*-9, *t*-11 and *t*-10, *t*-12; and 11.9 % other isomers	3 g/d sunflower oil		DB, R, PC	4
Nazare, 2007	France	44	28·9	25·2	3.76 g/d CLA-supplemented yoghurt-like products	(35:35) *c*9, *t*11/*t*10, *c*12	placebo yoghurts	36	DB, R, PC	3
Norris, 2009	Germany	35 obese postmeno-pausal women with type 2 diabetes	59.7	36.6	8 g/d, CLA-mix	(41.6:40.4) *c*9, *t*11/*t*10, *c*12	8 g/d, safflower oil	48	DB, R, crossover	5

▶ **Table 1** Demographic characteristics and baseline parameters of the included studies.

Author, and publication year	Location	Sample size and population	Mean age	BMI	CLA dose and form (g/d)	Isomers	Placebo dose and form	Duration	Design	Jadad score
Petridou, 2003	Greece	Sixteen females, healthy sedentary nor-mal-weight and overweight	22·30	23.1	2·1 g/d, CLA-mix	*c*9, *t*11–*t*10, *c*12 (50:50)	2·1 g/d, soyabean oil	6.5	DB, R, PC, crossover	4
Lopez-Plaza, 2013	Spain	38 male and female, healthy overweight	44	28.87	3 g/d CLA added in 200 mL skimmed milk	(50:50) *c*9, *t*11/*t*10, *c*12	200 mL skimmed milk without added CLA	24	DB, R, PC, Parallel	2
Riserus, 2002	Sweden	58 Obese men with the metabolic syndrome	52.15	27.87	3.4 g/day of CLA (isomer mixture) a 3.4 g/day of purified *t*10, *c*12 CLA b	(35.4:35.9) *c*9, *t*11/*t*10, *c*12 a 76.5% *t*10 *c*12 CLA b	placebo	12	DB, R, PC, Parallel	2
Shadman, 2013	Iran	56 in male and female overweight type2 diabetics	45.1	27.4	3 g/d, CLA-mix with Vit E placebo	(50:50) *c*9, *t*11/*t*10, *c*12	CLA placebo (soy bean oil) and Vit E placebo	8	DB, R, PC, Parallel	2
Syvertsen, 2007	Norway	41 male and female, healthy overweight	49	30.8	4·5 g/d, CLA-mix	*c*9, *t*11–*t*10, *c*12 (37·5:38·0)	4.5 g olive oil	24	DB, R, PC	2
Taylor, 2006	England	40 males, healthy overweight and obese	46	35	4·5 g/d, CLA-mix	*c*9, *t*11–*t*10, *c*12 (35:36) *c*9, *c*11–*c*10, *c*12 (1–2%) *t*9, *t*11–*t*10, *t*11 (1·5%) *t*8, *c*10–*c*11, *t*13 (<1%)	4·5 g/d, olive oil	12	DB, R, PC, Parallel	5
Watras, 2007	USA	40 male and female, healthy overweight	33	27.8	3.2 g/d CLA-mix	(39.2:38.5) *c*9, *t*11/*t*10, *c*12	4 g/d safflower oil	24	DB, R, PC, Parallel	2
Zhao, 2009	China	80 obese male and female with stage 1 uncontrolled essential hypertension	62.3	32.3	4·5 g/d, CLA-mix	(50:50) *c*9, *t*11/*t*10, *c*12	NA	8	DB, R, PC, Parallel	1



▶ **Fig. 2** Forest plot displaying mean difference and 95 % confidence intervals for the impact of CLA supplementation on plasma leptin concentrations (upper plot). Lower plot shows leave-one-out sensitivity analysis (lower plot).

Pooled estimate of CLA supplementation on plasma leptin concentrations

Meta-analysis of data from 26 treatment arms showed a reduction but not significant alteration in plasma leptin concentrations following CLA supplementation (WMD: −0.38 ng/ml, 95 % CI: −1.08, 0.32, p = 0.286); with significant heterogeneity among the studies (Q = 53.41, I2 = 53.20 %, p = 0.001) (▶ **Fig. 2a**). The pooled effect

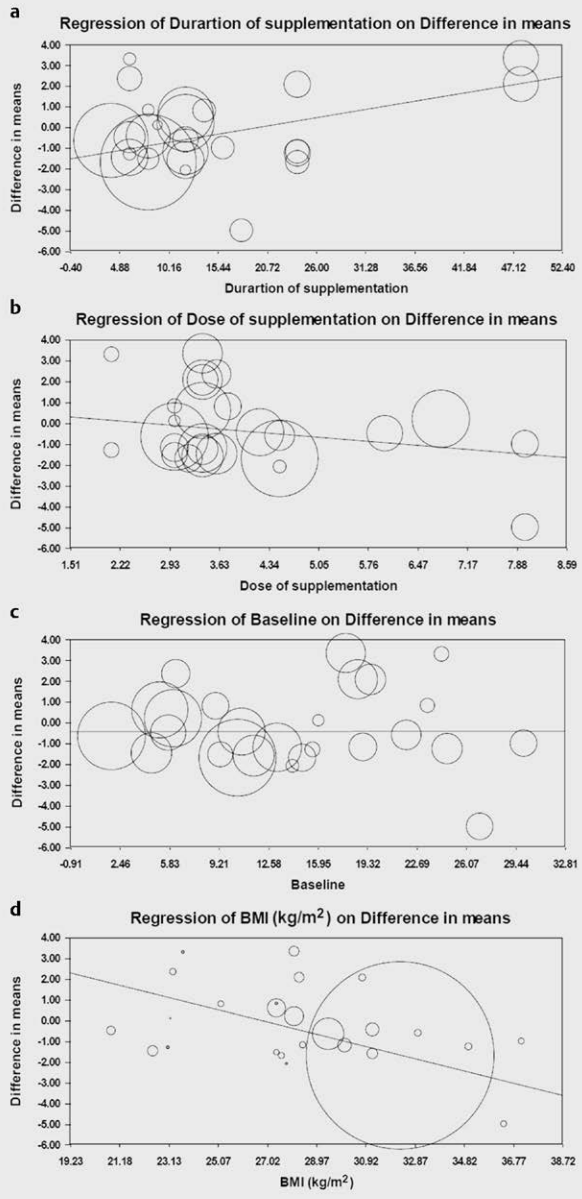
▶ **Table 2** Pooled estimates of effects on CRP within various subgroups.

Group	No. of Comparisons	Net Change (95 % CI)	p	p-Heterogeneity	I^2 (%)
Total	24	−0.29 (−1.11, 0.51)	0.476	0.001	53.24
BMI					
BMI ≥ 30	8	−1.47 (−2.15, −0.79)	< 0.001	0.345	10.99
BMI < 30	18	−0.10 (−0.66, 0.45)	0.723	0.473	0.00
Baseline leptin					
≥ 20 ng/ml	11	−1.40 (−3.33, 0.51)	0.152	0.17	28.26
< 20 ng/ml	13	−0.24 (−1.01, 0.52)	0.536	0.04	41.13
CLA dose					
≥ 3.5 g	12	−0.62 (−1.58 to −0.33)	0.201	0.013	54.00
< 3.5 g	12	−0.15 (−1.05, 0.73)	0.730	0.281	15.78
Intervention duration					
≥ 24 weeks	5	0.96 (−0.77, 2.71)	0. 135	0.182	33.90
< 24 weeks	19	−0.76 (−1.40, −0.12)	0. 019	0.047	37.55
Type of RCTs					
Parallel design	22	−0.26 (−1.02, 0.50)	0.506	0.001	58.77
Cross-over design	4	−1.17 (−3.13, −0.77)	0.237	0.338	11.85
Mean age					
≥ 40 years		−0.30 (−1.34, 0.73)	0.567	< 0.001	66.01
< 40 years		−0.56 (−1.28, 0.14)	0.120	0.940	0.00
Type of intervention					
CLA supplement	23	−0.37 (−1.14, 0.38)	0.335	< 001	56.95
CLA-enriched food	3	−0.37 (−2.10, 1.35)	0.673	0.810	0.00
Gender					
Female	7	−0.95 (−2.89, 0.99)	0.337	0.319	14.56
Male	7	−0.40 (−1.00, 0.19)	0.186	0.629	0.00
Both	11	0.03 (−1.38, 1.44)	0.966	0.004	61.59
Study quality					
≥ 4	16	−0.48 (−1.04, 0.07)	0.092	0.715	0.00
< 4	10	0.27 (−1.31, 1.87)	0.732	0.002	65.42

size was robust and remained non-significant in the leave-one-out sensitivity analysis (▶ **Fig. 2b**).

Sub-group analysis

Considering that the basal levels of leptin, type of study design (parallel or crossover design), intervention dose, study quality (measured with the Jadad score), study duration, sex composition, age, body mass index (BMI), sample size, and type of intervention may influence the net changes of leptin, we conducted meta-regression analysis based on these variables and found that the intervention duration (p = 0.00038), and baseline BMI (p = 0.0002), contributed to the heterogeneity among studies. We categorized studies based on subjects' body mass index (BMI) status and duration of supplementation. Subgroup analysis based on BMI status showed that CLA can significantly reduce leptin when used in obese subjects (WMD: −1.47 ng/ml, −2.15, −0.79, p < 0.001); whereas the overall effect for studies in nonobese subjects was not significant (WMD: −0.10 ng/ml, 95 % CI: 0.66, 0.45, p = 0.723). When the studies were stratified according to their duration, there was a significant greater effect on leptin levels in the subset of trials with < 24 weeks of duration (WMD: −0.76 ng/ml, 95 % CI: −1.40, −0.12, p = 0.019) versus the subset lasting ≥ 24 weeks (WMD: 0.96, 95 % CI: −0.77, 2.71, p = 0.135). With respect to baseline leptin levels, a greater but not significant reductions was found in the studies including subjects with baseline leptin ≥ 20 ng/ml levels (WMD: −1.40, −3.33 to 0.51, p = 0.152) but not in the studies enrolling subjects with lower initial concentrations (WMD: −0.24, −1.01, 0.52, p = 0.536). When the studies were categorized according to the dose of supplementation, there was a greater leptin-reducing effect in trials with ≥ 3.5 g/day (WMD: −0.62, −1.58 to −0.33, p = 0.201), but not with those < 3.5 g/day dosage (−0.15, −1.05, 0.73, 1.02, p = 0.730) (▶ **Table 2**). Among other pre-specified characteristics assessed as potential sources of heterogeneity, the effect of CLA on leptin appeared potentially stronger in trials with higher quality as assessed

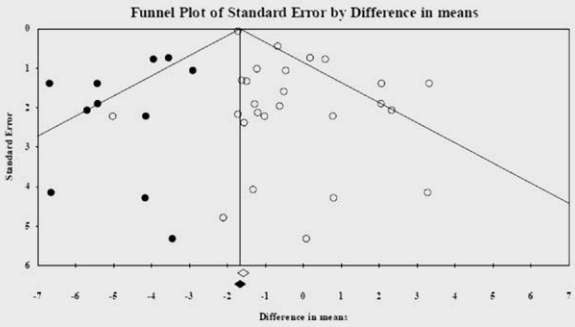


▶ **Fig. 3** Meta-regression plots of the association between mean changes in plasma leptin concentrations with duration of supplementation **a**, dose of supplementation **b**, changes in baseline serum leptin concentrations **c**, and change in baseline BMI **d**.

by Jadad scale. Additionally, we found a greater reduction of leptin in those younger than 40 years and those trials performed with crossover design (▶ **Table 2**).

Meta-regression

In meta-regression, changes in plasma leptin concentrations following CLA supplementation were found to be independent of dose of supplementation (slope: –0.27; 95 % CI: –0.75, 0.20; p = 0.265), and baseline leptin concentrations (slope: –0.0004; 95 % CI: –0.09, 0.09; p = 0.992); however, significant association was found with respect to treatment duration (slope: 0.075; 95 % CI: 0.02, 0.12; p = 0.0033) and changes in BMI baseline (slope: –0.30; 95 % CI: –0.41, –0.18; p < 0.001) (▶ **Fig. 3a-d**).



▶ **Fig. 4** Funnel plot displaying publication bias in the studies reporting the impact of CLA supplementation on plasma leptin concentrations.

Publication bias

Visual inspection of funnel plots suggested asymmetry in the meta-analyses of CLA and leptin that was confirmed by Begg's rank correlation test (Kendall's Tau with continuity correction = –0.23, z = 1.65, two-tailed p-value = 0.098) and Egger's linear regression test)intercept = 0.949, standard error = 0.258; 95 % CI = 0.41, 1.48, t = 3.67, df = 24, two-tailed p = 0.0011). After adjustment of effect size for potential publication bias using the trim and fill correction, 11 potentially missing studies were imputed in the funnel plot. The corrected effect sizes were calculated to be –1.66 (95 % CI: –1.80, –1.51) (▶ **Fig. 4**). The "fail-safe N" test showed that 140 studies for leptin would be needed to bring the effect size down to a non-significant (p > 0.05) value.

Discussion and Conclusions

To the best of our knowledge, the current systematic review and meta-analysis is the first to assess the current evidence from RCTs on the efficacy of supplementation with CLA on plasma leptin concentration. The results of this meta-analysis did not indicate a significant effect of CLA supplementation on leptin level. There was a significant heterogeneity among studies. According to meta-regression, changes in plasma leptin following CLA supplementation were significantly affected by baseline BMI and duration of intervention. CLA may significantly reduce leptin in trials shorter than 24 weeks and only when used for obese subjects. However, effect of supplementation on plasma leptin was more pronounced in those with higher baseline plasma leptin, or in studies with higher quality according to Jadad scale, or in higher doses, or in younger individuals, but all were insignificant. The results of current study did not change after omitting any study.

Moreover, the results of a study by Zhao et al. was in line with our study as they demonstrated the effects of CLA supplementation on reducing plasma leptin in obese individuals [51]. However, in other studies, no effects of CLA ingestion on circulating leptin was reported [52–54] that was in accordance with the overall results of current meta-analysis.

One possible explanation for the effects of CLA supplementation on circulating leptin might be due to the decrease in body fat following supplementation in obese individuals [51]. It is hypothesized that CLA can reduce body fat via affecting lipolysis and decreasing the activity of lipoprotein lipase, an enzyme important for fat deposition in adipose tissue [5]. On the other hand, according to animal studies, CLA supplementation might activate peroxisome-proliferator-activated receptor-γ (PPAR-γ), which in turn might decrease leptin gene expression [55]. While in human studies, sometimes, opposite effects of CLA supplementation on PPAR-γ were reported [56]. On the other hand, lack of effect of CLA supplementation on body weight or total body fat may partially explain the reason for the lack of overall effect on reducing plasma leptin [27]. Additionally, activity and dietary intake are important factors that might interfere with the effects of CLA supplementation on leptin level [57].

In addition, it is noteworthy to state that in a study the effect of CLA on reducing circulating leptin was obvious during the first weeks of intervention, but after several weeks and at the end of trial, no differences was demonstrated between the intervention and the control group regarding leptin concentration. They mentioned that despite the decrease in overall fat mass, effects of CLA ingestion on leptin level in long-term might be independent of changes in fat mass [22]. Another reason for the lack of reducing effect of CLA on leptin might be due to the increases in insulin levels after the initial weeks of CLA supplementation [22] that can increase leptin concentration and might blunt the decreasing trend. It was reported in some studies that changes in leptin concentration are correlated with changes of fasting plasma insulin independent of any changes in total fat or BMI. Increase in insulin level is equivalent to an increase in circulating leptin [14, 58]. Our meta-analysis confirmed this hypothesis that CLA ingestion might not affect concentrations of leptin in long-term and its effect on leptin concentration is independent of changes in body fat in long-term.

Our study has some strength such as the number of studies included in this meta-analysis that was acceptable. The heterogeneity in various studies included in this meta-analysis is due to differences in sample size, dose of intervention, duration of supplementation, baseline leptin concentration, and target population and we tried to assess their effects on changes in leptin concentration following CLA supplementation to have a better conclusion.

In conclusion, in this systematic review and meta-analysis, after reviewing all of the RCTs, overall, no effect of CLA supplementation was seen on leptin concentration. We found that the effects of CLA supplementation on circulating leptin might be more pronounced in obese individuals and in short-term supplementations. More RCTs with shorter durations on overweight or obese people are needed to be able to draw a better conclusion. Additionally, various animal and human studies are necessary to delineate possible mechanisms of action for CLA effects on adipocytokines, especially leptin.

Conflict of Interest

The authors declare that they have no conflict of interest.

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