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Co-Administration Effects of Conjugated Linoleic Acid and L-Carnitine on Weight Gain and Biochemical Profile in Diet Induced Obese Rats

Maryam Nazari, Majid Karandish, Alihossein Saberi

***Abstract*—**Obesity as a global health challenge motivates pharmaceutical industries to produce anti-obesity drugs. However, effectiveness of these agents is remained unclear. Because of popularity of dietary supplements, the aim of this study was tp investigate the effects of Conjugated Linoleic Acid (CLA) and L-carnitine (LC) on serum glucose, triglyceride, cholesterol and weight changes in diet induced obese rats. 48 male Wistar rats were randomly divided into two groups: Normal fat diet (n=8), and High fat diet (HFD) (n=32). After eight weeks, the second group which was maintained on HFD until the end of study, was subdivided into four categories: a) 500 mg Corn Oil (as control group), b) 500 mg CLA, c) 200 mg LC, d) 500 mg CLA+ 200 mg LC.All doses are planned per kg body weights, which were administered by oral gavage for four weeks. Body weights were measured and recorded weekly by means of a digital scale. At the end of the study, blood samples were collected for biochemical markers measurement. SPSS Version 16 was used for statistical analysis. At the end of 8th week, a significant difference in weight was observed between HFD and NFD group. After 12 weeks, LC significantly reduced weight gain by 4.2%. Trend of weight gain in CLA and CLA+LC groups was insignificantly decelerated. CLA+LC reduced triglyceride level significantly, but just CLA had significant influence on total cholesterol and insignificant decreasing effect on FBS. Our results showed that an obesogenic diet in a relative short time led to obesity and dyslipidemia which can be modified by LC and CLA to some extent.

***Keywords*—**Conjugated linoleic acid, high fat diet, L-carnitine, obesity.

I. Introduction

OBESITY as one of the most challenging health problems has nearly doubled between 1980 and 2008 [1], [2] which is followed by serious medical, social, and psychological consequences. Regarding the high global prevalence of obesity, it is estimated that 1-10% of health costs are contributed to obesity comorbidities. If instant action is not taken, millions will endure from a set of serious health disorders [3], [4].

Different strategies have been used to manage obesity including diet, exercise, behavior modification, medications and surgery. Although pharmacotherapy may produce a more rapid weight loss, they must be used along with other approaches not instead of them. Meanwhile, approved drugs for management of obesity are limited in variety and long-term effectiveness for having significant side effects such as hypertension, insomnia, diarrhea and flatulence. That is why dietary supplements have been attracted lots of attention due to their naturality and availability in order to use in weight loss [5], [6].

Blanck et al. reported that 7% of adults used over the counter (OTC) weight-loss supplements which were more common among young obese women. These products are popular for being natural, easily accessed, less demanding than accepted lifestyle changes and inflated advertising claims [7], [8].

Fat burner refers to categories of nutritional supplements that are claimed to increase energy expenditure by enhancing fat metabolism and oxidation, decreasing fat absorption, prevention of weight regains after weight loss and/or increasing weight loss [9]. LC and CLA are among the most common fat burner supplements.

LC, a non-essential amino acid which is synthesized from the essential amino acids lysine and methionine, is available in different types of meats and dairy products. LC is extensively applied in the diet as a factor responsible for translocation of long chain fatty acids into the mitochondria matrix [10], [11]. It seems that, in carnitine deficient situations, most of the dietary lipids cannot be metabolized as an energy source and our body would aggregate fatty acids which may result in obesity [12], [13]. Wutzke and Lorenz showed that LC supplementation led to a significant increase in beta-oxidation of fatty acids without any changes in protein synthesis and breakdown rates in slightly overweight subjects [14]. Long term administration of LC for combatting obesity is considered safe in comparison to the previous traditional medications [5]. Despite wide use of LC for obesity management, there is inconsistent evidence that it does alter fuel metabolism or enhances weight loss in healthy subjects.

CLA, a group of positional and geometric isomers of linoleic acid with conjugated double bonds, seems to act as an anti-obesity mediator [9]. CLA effects on body fat were first described almost 27 years ago in mice, and research has since confirmed these findings to some different degrees, based on animal type and CLA isomer [15]. The results in human have shown that the magnitude of CLA effect is, however,

Maryam Nazari is with the Nutrition and Metabolic Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (corresponding author, phone: 00989121580731; e-mail: Maryam.Nazary1@yahoo.com)
Majid Karandish is with the Nutrition and Metabolic Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (e-mail: mkarandish@yahoo.com)
Alihossein Saberi is with Department of Medical Genetic, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (e-mail: ahsaberi70@hotmail.com).

negligible and does not seem to be clinically important (less than 5% weight loss from baseline) [16].

Though LC and CLA supplements as weight loss agents have a widespread use nowadays [9], administration of them for reducing body fat, has remained a controversial subject.

Although different molecular targets for both treatment and prevention of obesity have been introduced, targeted monotherapy has not shown successful effects. Thus, targeting multiple metabolic pathways simultaneously with several natural compounds to attain synergistic or additive effects might be a hopeful approach to address obesity.

While CLA and LC are structurally different compounds, there is a close inter-relationship between them in fat metabolism. A few studies have clarified the similar or complementary role of CLA and LC in metabolism [17]. In addition, several researches have investigated single effect of these two supplements in obesity management but potential effects of combined CLA and LC on obesity have not been studied yet. Such idea has been reported in a patent [18] but to the best of our knowledge no study on this topic has done before our project. The present study had an experimental design to compare the separate effects of LC and CLA with combination of them on weight gain and some related biochemical factors in diet induced obese rats. HFD was used to create the obesity model in rats.

II. Materials and Methods

A. Animals and Diets

48 male albino rats of Wistar strain from Laboratory Animal Unit of Jundishapur University of Medical Sciences, Ahvaz, Iran weighing 150-200 g were housed in groups of four per cages and maintained on a 12-hour light: dark cycle at 22 °C and the relative humidity at 50±5%. The animals that aged 8 weeks were placed on normal chow diet for the first week for acclimation with new environmental conditions. Then they were randomly assigned into three different diets:

- Chow diet (CD) all over the study (n=8)
- Normal Fat Diet (NFD) all over the study (n=8)
- HFD all over the study (n=32)

The obesogenic diet was a modification of the AIN-93 Purified Diets for Laboratory Rodents [19]. Different ingredients of the original diets were purchased and mixed. Cellulose was replaced by wheat bran in formulation in this study and margarine was added in place of a proportion of corn starch to reach 60% of diet from fat. Details about the proportional composition of each group-specific diet are listed in Table I. Animals had free access to food and water. Body weight was measured and recorded weekly by means of a digital scale (MFD By OHAUS CORP, Florham Park N.J.).

The rats were fed HFD for eight weeks, prepared freshly twice a week and stored in 4°C. On the 8th week, HFD group was randomly subdivided into four categories (n=8 in each) to receive the main interventions as follows for four weeks:

1. Control group, which received HFD + 500 mg per kg body weight corn oil.
2. CLA group, which received HFD + 500mg per kg body weight CLA as a 50:50 isomer blend of c-9, t-11 and t-10, c-12 CLA.
3. LC group, which received HFD + 200mg per kg body weight LC.
4. CLA+LC group, that received HFD + 500mg per kg body weight CLA+ 200mg per kg body weight LC.

TABLE I
Modified* American Institute of Nutrition Diet Composition

Ingredients	1 kg NFD (gr)	1 kg HFD (gr)
Corn starch	397	141
Casein	200	200
Dextrinized corn starch	132	68
Sucrose	100	52
Soybean oil	430	70
Fiber	50	50
Mineral mix	35	35
Vitamin mix	10	10
L-Cystine	3	3
Choline bitartrate	2.5	2.5
Tert-butylhydroquinone	0.01	0.01

*AIN-93 Purified Diets for Laboratory Rodents [19] was modified. Fiber was replaced by wheat bran in formulation.

The CLA used in this study was Tonalin (Natural Factors, USA) which contains free fatty acids containing about 80% CLA. LC was Levocarnitin (So.Se PHARM, Italy) which contains 1gr LC per 10ml solution.

At the beginning of 12th week all rats were fasted for 10 h before anesthetization with Ketamine-xylicin and then blood was collected from the vena cava (heart) into a centrifuge tube and allowed to clot to obtain the serum. Serum was separated from samples after centrifugation at 4000 rpm for 10 minutes at 4 °C. All samples were stored at -70 °C until biochemical analyses.

This experiment was carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised 1996 and the guidelines provided by the ethical committee of experimental animal care at Jundishapur University of medical sciences (NRC9204).

B. Biochemical Analyses

Serum total cholesterol (TC), triglyceride (TG), and fasting glucose concentrations were measured on HITACHI 911 chemistry analyzer using colorimetric test supplied by Bionik Diagnostic Systems (Tehran, Iran).

C. Statistical Analyses

All statistical tests were performed with the use of SPSS (Statistical Package for Social Sciences version 13.0; SPSS Inc, Chicago) and a $p < 0.05$ was statistical significance level. Results are expressed as means ± standard error of the mean (SEM). Normality and homogeneity of variance was tested with Kolmogrov-Smirinov. One-way ANOVA, followed by LSD test were used to compare mean differences in body weights and biomedical factors.

III. Results

A. Weight Changes

Body weights at the baseline were not different between CD, NFD and HFD groups. At the end of 8th week, weights increased significantly in rats on the HFD compared with controls (Table II). HFD-induced obese rats weighed 8.5% and 20% more than rats in chow and NFD groups, respectively. Treatment with LC after four weeks significantly reduced weight gain during the treatment period. Trend of weight gain in CLA and LC+CLA groups was decelerated in comparison with HFD group; however it was not statistically significant (Table III).

B. Biomedical Parameters

Study results showed that HFD did not lead to hyperglycemia. Nonetheless, CLA (not LC) showed a non-significant effect on reducing blood glucose. In addition, a slight descending trend was observed in LC+CLA group in comparison with HFD group (Fig. 1).

CLA and LC modified serum TC levels. This effect was statistically significant ($P < 0.05$) in CLA group. LC and LC+CLA, had no considerable effect on TC levels (Table IV). TG levels in CLA and LC groups, were significantly lower than CD, NFD and HFD groups ($P < 0.05$). However, CLA+LC had marginal-insignificant effect on TG levels (Table V).

TABLE II
Effect of CD, NFD and HFD on Body Weights in Eight Weeks

Group	n	Baseline weight	P	Eight-week weight	P
CD	8	163.88 ± 5.74		272.13 ± 9.92	
NFD	8	170.00 ± 3.91	0.26†	246.38 ± 6.48	0.031‡
HFD	32	176.04 ± 4.02		295.43 ± 5.36	0.000§

Values are expressed as means ± standard error. †: insignificant weight difference between CD, NFD and HFD at baseline. ‡: significant weight difference between CD and HFD at eighth week. §: significant weight difference between NFD and HFD at eighth week.

IV. Discussion

The present study was designed to gain more insight into the effects of co-administration of CLA and LC on weight changes and their potential benefits in modifying serum lipid profile and glucose. We aimed to achieve obesity model by feeding a semisynthetic HFD in eight weeks following by combination therapy for four weeks in Wistar rats. This model simulates a tangible clinical case of obesity and its treatments that its duration is safe and recommended in previous investigations [20].

Despite the reported positive effects of LC and CLA on body weight, no additive or synergistic effect on weight control was observed in this experiment. However, Chopra reported such synergistic activity in treating overweight and obesity [18].

According to the past studies, LC keeps its anti-obesity effect when it is administered in combination with other compounds like arginine, caffeine, soy isoflavones [21], extract of Garcinia Cambodia [22] and herbal mixture extract [20]. This effect of LC might be mediated via induction of lipolysis, fatty acid oxidation and down-regulation of both PPARγ and adipose-specific fatty acid binding protein (aP2) adipogenesis [23]. In spite of evidence and a few relevant proposed mechanisms about positive effects of LC on fat metabolism, the study of Villani et al. (no fat mass or weight loss after eight weeks of LC administration accompanied by aerobic training in moderately obese women) made the relationship doubtful [24].

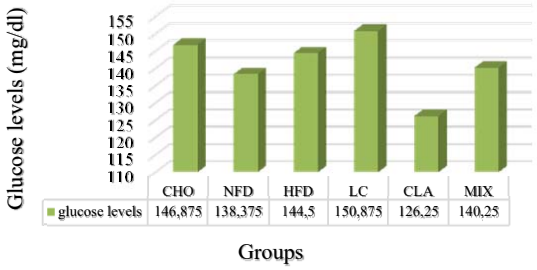

Fig. 1 Glucose levels (mg/dl) the end of study MIX: LC+CLA

Some studies showed that LC can exacerbate symptoms of hypo-thyroidism as it might inhibit thyroid hormone entry into the nucleus of cell [25], and thus, it can act as a peripheral antagonist of thyroid hormone action [26], [27]. In this way, it will lower metabolic rate which may lead to inefficiency of LC in weight loss and other related parameters.

Even though available data about the effect of CLA on body fat is not completely understood, different mechanisms have proposed for possible anti-obesity effects of CLA, including lipolysis augmentation, promotion of preadipocyte apoptosis via increase of TNFα mRNA and increase of uncoupling protein 2 (UCP2), adipogenesis inhibition and reduction of preadipocyte differentiation are notable [28]– [30].

Our results confirmed that LC limits weight gain in rats fed HFD in comparison with control group (7.5% vs. 12%, respectively) and unexpectedly did not show such effect for CLA or LC+CLA. The only indicator of weight change in our study was body weight whereas body fat is a more sensitive criterion for assessing obesity in animals. Rats fed HFD (40% of energy) for 10 weeks developed 10% increase in total body weight while 35–40% increase in total body fat. The source of dietary fat may affect the results; SFA of plant origin might not be as effective as SFA of animal origin in developing obesity [31].

The effects of CLA on glucose metabolism have not been clearly explored. Some studies have reported that CLA enhances glucose tolerance and insulin metabolism in Zucker fa/fa or Sprague–Dawley rats, while some others have shown insulin-resistance properties for CLA in C57BL/6J mice [32], [33]. On the other hand, LC effects on improvement of the insulin-resistant state is well established [34], [35]. In our current work as mentioned by Ishii [36], the HFD did not significantly increase serum glucose levels that may be related to fat source. However, we observed a 12% reduction in FBS just in CLA group that could be attributed to its role in

inducing fat metabolism and insulin sensitivity. It would be better to assess insulin concentrations and/or HOMA-IR to do a more precise judgment. Furthermore, our study failed to indicate an additive effect of CLA + LC on glucose metabolism (Fig. 1).

TABLE III
EFFECT OF LC, CLA AND LC+CLA ON BODY WEIGHT AND WEIGHT GAIN RATE DURING FOUR WEEKS IN OBESE RATS

Group	n	Eight-week weight	Twelve-week weight	difference	p
CD	8	272.13 ± 9.92	299.25 ± 11.22	27.12(9.97%)	
NFD	8	246.38 ± 6.48	271.62 ± 8.03	25.2(10.2%)	
HFD (control)	8	297.12 ± 13.16	336.43 ± 15.10	35.12(11.8%)	0.047†
LC	8	294.38 ± 7.60	316.68 ± 11.8	22.5(7.6%)	0.08‡
CLA	8	288.71 ± 8.27	312.71 ± 9.62	24(8.3%)	
LC+CLA	8	285.86 ± 6.19	310.86 ± 7.43	25(8.7%)	0.12§

Values are expressed as means ± standard error. †: significant difference between LC and control HFD in weight gain during four weeks (P=0.047). ‡ and §: insignificant difference between CLA and LC+CLA with control HFD in weight gain during four weeks (P=0.08 and 0.12 respectively).

Adverse effects of CLA on lipid profile have been reported in a few studies that were attributed to its oxidant properties, reduction of cellular uptake of lipids from the blood and total antioxidant defenses [37]. In line with other studies [20], [38], [39] in our study CLA and LC supplementation improved serum TG. TC level was just affected by CLA, but no additive or synergistic effect was observed in combination of LC and CLA.

The possible explanation may be short period of the study and using HFD as the comparative group (in some other studies CD was used for comparison). Our experimental semi-synthetic diet triggered mild metabolic disorders and obesity. Thus, it failed to result in significant differences in some variables between NFD and HFD groups.

TABLE IV
EFFECT OF LC AND CLA ON SERUM TC LEVELS

Group	n	12 weeks Cholesterol (mg/dl)	P
CD	8	76.00 ± 4.74	
NFD	8	86.62 ± 3.45	
HFD (control)	8	86.62 ± 3.17	
LC	8	78.38 ± 3.94	
CLA	8	71.25 ± 4.03†	
LC + CLA	8	80.50 ± 2.67	0.006

Values are expressed as means ± standard error. † TC levels in CLA group was significantly less than NFD and HFD (control) groups (P=0.006).

Interesting point in our study was that LC preventing effect on weight gain was stronger than CLA and significant but in other variables CLA had stronger effects. Co-administration of them in all variables showed insignificant-stronger effect than LC but weaker than CLA.

Nature and proportion of the dietary fat, duration of treatment, mixed isomer form of CLA and animal species might affect the lipid-lowering, insulin resistance and energy expenditure roles of LC and CLA [33]. According to the available data, glucose-lowering effect of CLA in mice is stronger than rats. We used polyunsaturated fats (soybean oil) and saturated fat (margarine instead of lard) in our experimental diets that in turn interfere with dyslipidemia in comparison to diets which are converted to high fat by lard and cholesterol. Inconsistency of results might come from improper ratio of CLA to LC that was 2 in our experiment. Also, ineffectiveness of simultaneous use of CLA and LC may be related to hypothyroid properties of LC.

Extrapolation of such study to human needs to be further investigated, modifying study design may result in more accurate evidence: for example, longer intervention period, using different isomers of CLA, survey of dose dependent relationship (both CLA and LC) and assessment of food intake are some of our suggestions.

TABLE V
EFFECT OF EIGHT WEEKS TREATMENT WITH LC AND CLA ON SERUM TG LEVELS IN RATS

Group	n	Twelve-week TG (mg/dl)	P
CD	8	103.25 ± 15.95	
NFD	8	115.62 ± 9.82	
HFD (control)	8	108.75 ± 13.10	
LC	8	73.50 ± 8.53	0.073 0.013† 0.035‡
CLA	8	63.25 ± 10.22	0.018* 0.002** 0.007***
LC + CLA	8	87.62 ± 9.29	

Values are expressed as means ± standard error. † LC in comparison to NFD and (‡) HFD groups, lower serum TG concentration (p = 0.013 and 0.035 respectively). *CLA in comparison to CD, (**) NFD and (***) HFD groups, lower serum TG concentration (p = 0.018, 0.002 and 0.007 respectively). But significant synergistic effect was not detected (p > 0.05).

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