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The Potential Effect of Conjugated Linoleic Acid on Endurance Exercise: A Mechanistic Review

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Abstract

Introduction: The purpose of the present study was to appraise the results from disseminated human, animal and *in vitro* studies, and evaluate the possible effect along with the mechanism of CLA supplementation on endurance exercise.

Methods: Related articles were searched on PubMed, Web of Science, Scopus, Embase, and Cochrane databases with defined keywords. Articles were assessed through their titles and abstracts. Finally, 11 articles were included based on inclusion and exclusion criteria.

Results: Most of the studies were conducted on animals, and CLA was often supplemented along with training. Dosage and study duration vary for a broad range. Results showed various possible pathways on the effect of CLA supplementation on endurance exercise and related factors.

Conclusions: It was indicated that CLA supplementation could prolong endurance performance by improving oxidant status, mitochondrial biogenesis, testosterone biosynthesize, fat oxidation, and change in body composition. Although CLA is being used in many countries and numerous studies have shown its safety, its long-term supplementation and effect need to be investigated. Also, further studies are required to identify the molecular mechanism in the human body.

Keywords: CLA; Endurance Exercise; Conjugated Linoleic Acid; Resistance Exercise; Oxidant Status; Mitochondrial Biogenesis; Testosterone

Introduction

Exercise is generally divided into two groups: aerobic/endurance and power/strength [1]. Endurance exercise such as running, swimming and cycling and is classically performed against a relatively low load over a long duration, whereas strength exercise like bodybuilding is performed against a relatively high load for a short period [1,2]. However, a pure type of each exercise type is rare, and exercises are usually a mixture of both types that have been termed concurrent exercise. In response to exercise, our body can adapt to either endurance or strength exercise. Low-intensity training for long periods can enhance individuals' endurance performance adaptations, resulted from improved cardiovascular system function [1].

The power and velocity maintained for a duration of 30 minutes to four hours evaluate the endurance performance typically [3]. Accumulation of hydrogen ion (i.e., lactic acidosis) and heat (i.e., hyperthermia) are the main by-products of extreme and prolonged oxidative metabolism come along with endurance exercise [3]. It is also suggested that oxidative stress can be induced during exercise, especially when training is of high intensity. In fact, oxygen-containing free radicals such as the hydroxyl ions, superoxide, hydroperoxyl, and lipid peroxyl are the metabolites generated after exercise. Whenever the production of these radicals exceeds the antioxidant capacity of the tissue, the radicals quickly react with cellular components. As a result, this oxidant system leads to reduced contractile function, arrhythmias, and muscle fatigue [4]. Whether the body has the potency to supply enough oxygen and glucose is another crucial determinant of endurance exercise [3].

Conjugated Linoleic Acid (CLA) is a term used to describe a group of positional and geometrical isomers of conjugated dienoic octadecadienoate fatty acids produced from linoleic acid by rumen bacteria [5]. CLA contains two double bonds separated by a single bond in either a configuration of cis or trans [6]. All physiological effects are induced by cis-9, trans-11, and trans-10, cis-12 (c9:t11 and t10:c12, respectively) isomers which are among the most common isomers of CLA [7]. These double bonds are commonly positioned between carbon molecules 8 and 13, but they can be located in any position on the carbon chain [8]. Also, the effect was reported to be dose-dependent in the range of dietary CLA levels between 0 and 1.5% weight to accomplish desired health benefits [6]. The two major sources of CLA in human diets are dairy products (milk and cheese) and ruminant meats (beef and lamb) [9]. The fat in meat and milk contains about 4.3 and 5.5 mg CLA/g of fat respectively with almost 9-cis and 11-trans isomers [6]. The potent biological effect of CLA such as anti-carcinogenic, anti-inflammatory, anti-obesity, anti-diabetic, immunomodulatory, anti-atherosclerotic, reduction of whole-body fat and bone formation promoting properties have been suggested in previous studies [10]. Also, studies demonstrate the effects of CLA supplementation on the energetic metabolism, promoting significant changes in the lipid metabolism and in body composition [11]. Studies suggest that CLA supplementation may also help re-synthesize of glycogen and improve fatty acid b-oxidation in skeletal muscle [11]. Therefore, we have conducted this review to evaluate

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Table 1: Conjugated Linoleic Acid effects on endurance exercise.

Type of study	Author/date	Supplementation/dosage	Model	Results after CLA supplementation
Animal	R Barone et al., [12] 2017	CLA/ 0.7g/kg/day as a food supplement and 35 microliters of sunflower oil as placebo	Mice assigned into four groups: 1. placebo sedentary 2.CLA sedentary 3. placebo trained 4.CLA trained, receiving placebo and CLA for six weeks	No significant change: stimulation of PGC1a isoforms Increased: hypertrophy of type IIx muscle fibers
	D Kwon et al., [13] 2017	1% CLA from dietary fat	Rat divided into three groups: 1. HFD sedentary 2. CLA supplemented sedentary 3. CLA exercise	Significant decrease: MDA content, Significant increase: increasing Cu, Zn-SOD and Mn-SOD expression levels in the SOM
	Y Kim et al., [14] 2016	0.5% CLA diet (37.8% cis-9, *trans*-11, 37.6% *trans*-10, cis-12 and 5.3% other CLA isomers) and soybean oil as control	Mice were divided into four groups: 1. sedentary control 2. exercise control 3. sedentary CLA 4. exercise CLA	Significantly reduced: BW, BFM, Significant increased: SIRT1 and PPARγ coactivator-1a, endurance capacity, induction of genes associated with muscle fibers
	K Cho et al., [15] 2016	1% CLA (36.8% *cis*-9, *trans*-11 CLA, 37.8% *trans*-10, *cis*-12 CLA, and 1.2% *trans*-9, *trans*-11 CLA)	Rats divided into three groups: 1.HFD sedentary group 2. 1% CLA supplemented HFD, sedentary group 3. 1% CLA supplemented HFD, exercise group	Significant increase: PPARγ expression, GLUT-4 protein expression, HDL Significant decrease: LDL, TG, TC, glucose, insulin, HOMA-IR
	R Barone et al., [16] 2013	CLA/ 0.7g/kg/day as a food supplement and 35 microliters of sunflower oil as placebo	Mice assigned into four groups: 1. placebo sedentary 2.CLA sedentary 3. placebo trained 4.CLA trained, receiving placebo and CLA for six weeks	Increased: expression of CYP17A1leads to enhancing testosterone biosynthesis
	JH Kim et al., [17] 2012	0.5% CLA isomers from diet and normal diet as control	Mice divided into three groups: 1. Control 2. 0.5% cis-9, *trans*-11 CLA 3. 0.5% *trans*-10, cis-12	Significant increase: maximum running time and distance, glycogen content, PPARg Significant reduction: total adipose depots, TGs,
	Kim et al., [18] 2010	A diet containing 1% CLA and Normal diet as control	Two groups of mice received a standard diet and CLA containing diet for ten weeks	Significant reduction: BW, TG, urea nitrogen Significant improve: maximum running, liver glycogen,
	Mizunoya et al., [19] 2005	0.5% CLA from diet	Mice were divided into two groups: 1. Control diet 2. diet containing 0.5% CLA for one week	Significant increase: maximum swimming time, muscle lipoprotein lipase activity Significant reduction: respiratory exchange ratio
Human	Terasawa et al., [20] 2017	CLA/ 0.9 g/day as a supplement and magical Ace powder as placebo	Ten male athletes in a crossover study received CLA and a placebo for 14 days.	Significantly increased: BW, muscle mass, amount of exercise time, CFF, Significantly decreased: body fat percentage, RPE, creatine phosphokinase
	Colakoglu S [21] et al., 2006	CLA / 3.6 g/day and exercised for 30 min a day/ 3 times per week	Forty-eight females divided into four groups: 1. Exercise CLA 2. CLA 3. Exercise 4. Control	Significant reduction: serum glucose, BW, anthropometric indexes Significant increase: endurance performance (in exercise and CLA and exercise groups)
In vitro	Kim et al., [22] 2015	CLA isomers: cis-9, trans-11 (c9, t11) and trans-10,cis-12 (t10, c12)	Determination of CLA mechanism on mitochondrial biogenesis	Significant increase: phosphorylation of AMPK, NRF-1, Tfam, mitochondrial biogenesis
	Barone et al., [16] 2013	Different concentration of CLA	Identify the pathway which is stimulated by CLA supplementation in Leydig tumor Rat Cells (R2C)	Increased: expression of CYP17A1 which leads to enhancing testosterone biosynthesis

Abbreviation: CLA: Conjugated Linoleic Acid; PGC-1α: Peroxisome Proliferator-Activated Receptor Γ Coactivator 1α; PPARγ: Peroxisome Proliferator-Activated Receptor Gamma; BW: Body Weight; BFM: Body Fat Mass; CFF: Critical Flicker Frequency; RPE: Rate of Perceived Exertion; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance.

the possible effect and the mechanism of CLA supplementation on endurance exercise.

Methods

Articles evaluating "the effect of CLA and its isomers on endurance exercise" were searched on PubMed, Web of Science, Scopus, Embase, and Cochrane. The title and abstract of each article were assessed to delete duplication data. Any irrelevant articles were excluded. The remaining articles were reviewed to determine compatibility with the inclusion criteria. Searching was limited to articles with the English language. Review articles, case reports, letters, editorials, abstracts in symposium and congress, and unpublished studies were excluded. Studies meeting the following inclusion criteria were included: 1. English articles; 2. evaluated the effect of CLA isomers on endurance exercise. The following data were collected from each study: publication data (i.e., first author's name, publication year and study location), study design, sample size and specifications, intervention data (i.e., duration of intervention,

intervention substance and it's dosage, type and amount of placebo) and results related to our primary objective. Characteristic of studies have been summarized in (Table 1).

Results

We have evaluated eleven articles in this review. Results showed various possible pathways on the effect of CLA supplementation on endurance exercise and related factors. Most of the studies were conducted on animals, and CLA was often supplemented along with training. Dosage and study duration vary for a broad range. In the study of Barone et al., CLA supplementation was performed on groups of mice for six weeks with no change in the stimulation of the PGC-1isoform. However, it increased the hypertrophy of IIx muscle fibers [12]. Kwon et al., showed that administration of 1% CLA from dietary fat with or without exercise for eight weeks resulted in a significant decrease in MDA content and increased the expression levels of Cu, Zn-SOD, and Mn-SOD in Soleus Muscle (SOM) [13]. In another study, 0.5 CLA% from diet and soybean oil as a placebo was given to mice for four weeks, which CLA group resulted in a significant decrease in BW, BFM, and increased SIRT1 and PPARg coactivator-1a, endurance capacity, induction of genes associated with muscle fibers [14]. Also, in a study conducted in 2016, mice fed a high-fat diet and 1% CLA for eight weeks had increased expression of PPARg, GLUT-4 protein, HDL and decreased in LDL, TG, TC, glucose, insulin, HOMA-IR [15]. Barone et al. conducted a trial in which four groups of mice received 0.7g/kg/day CLA or sunflower oil as a placebo for six weeks. Ultimately, results from mice fed with CLA led to an increase in the expression of CYP17A1 and enhanced testosterone biosynthesis [16]. Kim et al., treated male rats with 0.5% trans-10, cis-12 CLA for six weeks, showed increased maximum running time and distance, glycogen content, PPARg, and a significant decrease in total adipose depots, TG [17]. In the study of Kim et al. Significant reduction in BW, TG, urea nitrogen, and improvement of maximum running liver glycogen were reported in 2 groups of mice that received a regular diet plus 1% CLA for ten weeks [18]. In another study, two groups of mice received 0.5% CLA for one week, which eventually showed an increase in maximum swimming time, muscle lipoprotein lipase activity, and decreased respiratory exchange ratio [19]. It was reported that consumption of 0.9g/day CLA by ten male athletes for 14 days significantly increased BW, muscle mass, amount of exercise time, Critical Flicker Frequency (CFF) as well as decreased body fat percentage, Rate of Perceived Exertion (RPE), creatine phosphokinase [20]. Also, Colakoglu S et al. demonstrated an increased serum glucose level, BW, anthropometric indexes, and decreased endurance performance (in exercise plus CLA group and exercise group) after a higher dose of CLA on men [21]. Supplementation with two CLA isoforms (t9, t11) and (t10, c12) showed a marked increase in the phosphorylation of mitochondrial biogenesis by Nff, 1, Tfam, AMPK [22].

Discussion

Mechanisms of CLA isomers affecting endurance exercise

Increased biogenesis of testosterone: It has been shown that a chronic increase in testosterone levels can have a significant increase in hypertrophy, strength, and may improve resistant training [23]. Multiple factors affect testosterone levels, including the time of the day, exercise, and diet. Several studies have investigated the effect of CLA with different dosages and duration [24,25]. These reports showed CLA effects on increasing lean body mass or decreasing fat mass by a slight increment in testosterone level [25]. Possible mechanisms have been concluded from studies. It was shown that treating R2C cells with CLA can increase the expression of CYP17A1 mRNA. CYP17A1 is one of the main proteins involving in steroidogenesis and directly affects the level of testosterone level. Increasing the CYP17A1 enzyme level in mice testicles lead to increased biogenesis of testosterone and induction of free plasma testosterone, which may play a vital role in steroidogenesis mediated by endurance exercise [16].

Increased fat oxidation: It is known that fat and carbohydrates are among the primary substrates in exercise [26]. However, fats provide a more considerable amount of energy (9 kcal per 1 gram), which makes them a better fuel for prolonged exercise [27]. Several studies have investigated the effect of CLA on fat oxidation [17,19]. Mizunoya et al. reported a significant increase in Lipoprotein Lipase (LPL) activity after CLA intake, which increased fat oxidation and endurance exercise capacity. Also, Kim et al., showed increased fat utilization leading to the improvement of maximum running time [19]. In another study, increased LPL activity leads to higher

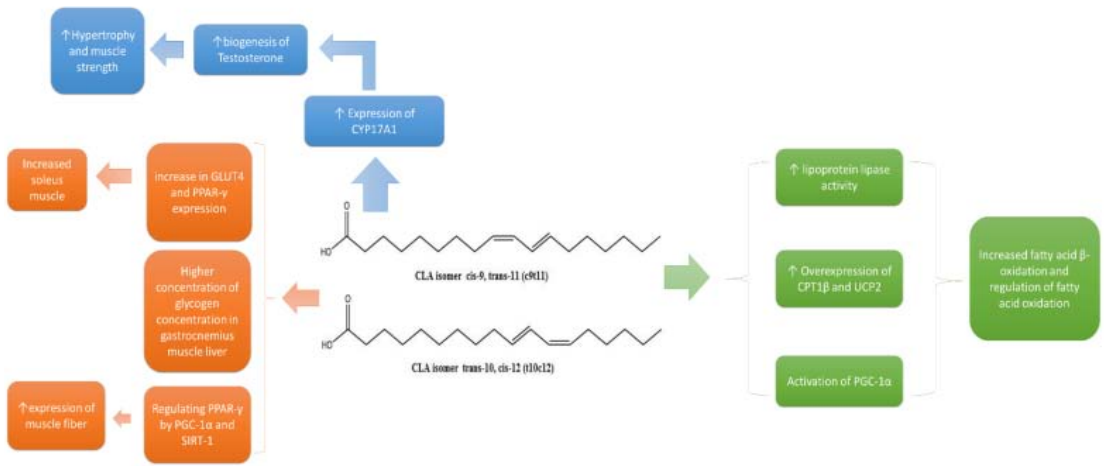

Figure 1:

triglycerides hydrolyzed by LPL. Fatty acids from hydrolyzed TG were taken by skeletal muscle, resulting in increased fat oxidation during exercise (Figure 1).

Furthermore, in a study by Kim et al., urea nitrogen level was lower in CLA-fed mice, which may reflect reduced protein metabolism and increased lipid metabolism in prolonged exercise. Also, it was reported that dietary *t10c12* CLA supplementation could up-regulate the mRNA expression of CPT1β and UCP2, while *c9t11* did not induce any significant change through these genes. Overexpression of CPT1β and UCP2 leads to increased fatty acid β-oxidation [17]. Another possible mechanism is the increased activation of PGC-1α, which could control the genes involved in the regulation of fatty acid oxidation. Overall, we conclude that CLA supplementation could improve endurance exercise capacity by increasing fat oxidation; however, more studies may be needed to clarify the exact mechanism in the human body.

Change in body composition: An increase in lean body mass, especially muscle mass and decrease in Body Fat Mass (BFM), is an adaptive way of the body to improve its capacity in resistance exercise. Results show that CLA supplementation caused a significant increase in body weight and a significant decrease in BFM, which indicates that increased body weight was caused by increased muscle mass. As previously mentioned, CLA intake increased testosterone level by over-expression of CPY17A1, and increased testosterone level is known to have a hypertrophic effect on skeletal muscle. Barone et al. demonstrated that CLA supplementation, along with exercise, could induce hypertrophy in type IIx fibers in plantaris muscles. Also, in another study, CLA caused an increase in GLUT4 and PPAR-γ expression in Soleus Muscle (SOM), which resulted in increased SOM mass. Regulating PPAR-γ by PGC-1α and SIRT-1 leads to the stimulation of mitochondrial biogenesis and induction of muscle fiber gene expression, which caused an increase in lipid metabolism and relative muscle weight. In a study by Kim et al., t10,c12 CLA fed-mice showed a higher concentration of glycogen concentration in gastrocnemius muscle and liver after 40 minutes of endurance exercise. This conservation of glycogen, accompanied by a decrease in TG and l-lactate concentration, suggests that CLA could enhance endurance capacity by increasing fat utilization and reducing the consumption of stored glycogen.

Increased mitochondrial biogenesis: The increase in capacity for resistant exercise is directly related to the higher oxygen extraction of the skeletal muscle, which is the result of the increased capillary to fiber ratio and improved mitochondrial concentration in the muscle [28,29]. It has been reported that CLA can increase mitochondrial biogenesis on several mechanisms. Kim et al. showed that t10, c12 isomer of CLA could improve mitochondrial biogenesis by an increase in AMP kinase and PGC-1α activity. Also, both isomers of CLA enhanced the expression of NRF-1, Tfam, and PPAR-γ, which all supporting that CLA supplementation could significantly increase mitochondrial DNA replication [14,22]. Cytochrome c, Cox IV and VDAC are several mitochondrial markers, which their expression can indirectly represent that the tissue or the cell is undergoing mitochondrial biogenesis [30]. Supplementation of CLA isomers (t11, c9, and t10, c12) demonstrated cytochrome c, and VDAC increased expression respectively, which again is an indicator of increased mitochondrial biogenesis and exercise capacity [22].

Improving oxidative status: Despite the health benefits of the exercise, many studies have indicated that endurance exercise can cause the induction of ROS overproduction [27,31-33]. This adverse event may lead to cellular damage. CLA supplementation showed antioxidant activity in several studies [13,34,35]. The possible mechanism may be due to increased expression of PPAR-γ, which is the regulator of oxidative metabolism and also activating AMPK [36]. In a study, CLA supplementation improved oxidative status by decreasing MDA content and increased expression of Cu, Zn, Mn-SOD in soleus muscle. Also, CLA caused the induction of ROS detoxifying enzymes such as SOD2 in mitochondria by increasing PGC-1α activity [13].

In conclusion, this mechanistic review overviews the literature investigating the role of CLA in exercise and has indicated that CLA supplementation can prolong endurance performance by improving oxidant status, mitochondrial biogenesis, testosterone biosynthesize, fat oxidation, and change in body composition. Although CLA is being used in many countries and numerous studies have shown its safety, its long-term supplementation and effect need to be investigated. Also, further studies are required to identify the molecular mechanism in human surveys.

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