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REVIEW

Impact of Conjugated Linoleic Acid (CLA) on Skeletal Muscle Metabolism

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Abstract Conjugated linoleic acid (CLA) has garnered special attention as a food bioactive compound that prevents and attenuates obesity. Although most studies on the effects of CLA on obesity have focused on the reduction of body fat, a number of studies have demonstrated that CLA also increases lean body mass and enhances physical performances. It has been suggested that these effects may be due in part to physiological changes in the skeletal muscle, such as changes in the muscle fiber type transformation, alteration of the intracellular signaling pathways in muscle metabolism, or energy metabolism. However, the mode of action for CLA in muscle metabolism is not completely understood. The purpose of this review is to summarize the current knowledge of the effects of CLA on skeletal muscle metabolism. Given that CLA not only reduces body fat, but also improves lean mass, there is great potential for the use of CLA to improve muscle metabolism, which would have a significant health impact.

Keywords CLA · Conjugated linoleic acid · Skeletal muscle metabolism · Obesity · Lean body mass · Physical activity

Abbreviations

ACC	Acetyl-CoA carboxylase
AMPK	AMP-activated protein kinase
BMR	Basic metabolic rate
CLA	Conjugated linoleic acid
CPT	Carnitine palmitoyltransferase
ERR	Estrogen-related receptor
FOXO	Forkhead box O
GLUT4	Glucose transporter type 4
IL-6	Interleukin 6
LPL	Lipoprotein lipase
MEF2	Myocyte enhancer factor 2
MHC	Myosin heavy chain
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NRF	Nuclear respiratory factor
PGC-1α	Peroxisome proliferator-activated receptor γ coactivator 1α
PPARδ	Peroxisome proliferator-activated receptor δ
RMR	Resting metabolic rate
SIRT1	Silent information regulator two protein 1
TAG	Triglyceride
TNF-α	Tumor necrosis factor α
UCP	Uncoupling protein

Introduction

The presence of conjugated linoleic acid (CLA, conjugated octadecadienoic acid) in milk was first reported in the 1930s, but it was not until the 1980s that CLA was shown to be a bioactive food component [1]. CLA is formed during the biohydrogenation of linoleic acid to stearic acid by rumen bacteria [2]. In addition, *trans*-11 vaccenic acid (another metabolite of biohydrogenation) is known to be converted

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to *cis*-9,*trans*-11 CLA by Δ^9-desaturase in the tissues [3]. Thus, the primary dietary sources of CLA are meats and dairy products from ruminants, although the overall CLA intake from food is not considered substantial [4]. It has been reported that CLA content ranges from 0.34 to 1.07 % of the total fat in dairy products, and 0.12 to 0.68 % in raw or processed beef [4]. In the United States, the average daily intake of CLA from food sources is 104–151 mg and 176–212 mg for women and men, respectively [5]. Accordingly, studies have reported serum CLA levels of approximately 20 μM, or 0.1 % of total fatty acids, in subjects with low dairy or meat consumption [6, 7], and approximately 50 to 180 μM with CLA supplementation of 0.8–3.2 g per day for 2 months [7].

There are at least 28 known CLA isomers. Among them, the *cis-9,trans-11* and *trans-10,cis-12* isomers have been the focus of studies on various biological effects of CLA [8]. The *cis-9,trans-11* isomer is a naturally predominant isomer, accounting for over 80 % of naturally occurring CLA [4]. In addition to the *cis-9,trans-11* isomer, the *trans-10,cis-12* isomer is found at very low levels in natural foods, but, when CLA is produced by chemical synthesis, this isomer is formed in significant amounts [8–10]. Currently, most commercial CLA preparations comprise almost equal amounts of *cis-9,trans-11* and *trans-10,cis-12* isomers, up to >90 % of total CLA, and these preparations are referred to as CLA mixtures or 50:50 mixtures.

CLA contains a *trans* configuration, and as there are known negative health issues associated with *trans* fat, some clarification with regard to CLA and *trans* fatty acids is warranted. The definition of *trans* fat labeling by the US Food and Drug Administration (FDA) is “all unsaturated fatty acids that contain one or more isolated double bonds in a *trans* configuration” [11]. It is clear, therefore, that CLA is excluded from "*trans*" fat product labeling, as it has a *trans* double bond that is conjugated, not isolated. Furthermore, in July 2008, the US FDA approved CLA mixtures for GRAS (generally recognized as safe) status in specific food categories, including fluid milk, yogurt, meal-replacement shakes, nutritional bars, fruit juices, and soy milk. Thus, it is expected that there will be an increase in CLA in foodstuffs, resulting in increased CLA intake for human health benefits.

CLA and Body Composition

Since 1997, with the discovery of the effects of CLA on body composition in a mouse model [12], numerous studies in various mammalian models have reported the effects of CLA supplementation on the modulation of body composition by reducing body fat and/or increasing lean body mass [8–10, 13–16]. While most studies in CLA have focused on the reduction of body fat, there is significant evidence supporting a concurrent increase in lean body mass, body proteins, or specific skeletal muscle mass [5, 8, 16, 17]. CLA was also confirmed to increase total protein content (not only %) as a representation of lean mass in animals [12]. Tables 1 and 2 summarize studies that have investigated changes in body composition in rodents. Of the two major isomers, the *trans-10,cis-12* CLA isomer significantly correlates with this effect [18–21]. Some researchers have suggested that CLA supplementation causes re-partitioning of the body composition, with fewer adipose depots and greater lean mass [22]. This observation was further supported in a pig model, where a CLA mixture fed to pigs at levels between 0.25 and 2 % of their diet acted as a re-partitioning agent to induce a reduction in back fat and an increase in lean body mass [23–27].

To date, there have been approximately 100 human studies investigating the regulation of body fat by CLA, and Table 3 summarizes only those in which changes in both body fat and lean body mass were reported. Compared to the results observed in animal models, CLA intervention studies in humans has yielded less substantial and more inconsistent results (Table 3). Among the clinical trials investigating the effects of CLA on both body fat and lean mass, five publications reported changes in both [28–32], while two studies reported increases in lean body mass with no effect on body fat [33, 34]. Schoeller *et al.* [35] performed a meta-analysis of 18 independent clinical studies assessing the effect of CLA on lean body mass, and concluded that CLA supplementation led to a relatively rapid onset of increased lean body mass, although the total increase was not remarkable (less than 1 %). This conclusion is further supported by a study of CLA in a mouse model [36], in which an increase in lean muscle mass preceded a reduction in fat mass. These observations suggest a potentially significant role of the muscle in the effects of CLA on body composition.

Mechanism of CLA-Mediated Change in Body Composition

Multiple mechanisms have been suggested to explain the effects of CLA on body composition [16, 17, 37]. These include CLA-mediated energy modulation, including reduced energy intake and enhanced energy expenditure, along with the inhibition of fat accumulation in adipose tissue.

The balance between energy intake and energy expenditure is important for proper weight regulation. Energy intake is from the food consumed, while energy expenditure is the sum of the basal metabolic rate (BMR), thermogenesis, and physical activity. First, with regard to CLA and energy intake, some studies have demonstrated that CLA-fed mice ate less food, whereas other studies have reported inconsistent results (Tables 1, 2) [38–43]. However, some

Table 1 Summary of mouse studies on conjugated linoleic acid (CLA) and body composition

References	Mouse		CLA supplementation			Results[e]				Muscle metabolism	
	Strain[a]	Gender[b]	Form[c]	Dosage (%)[d]	Duration	BW	BFM	LBM	Food intake	Energy expenditure[f]	Biomarkers[g]
Park *et al.* [12]	ICR	F + M	Mixture	0.5	4 weeks	–	↓	↑	↓		↑ CPT
West *et al.* [51]	AKR/J	M	Mixture	1.0–1.2	6 weeks	↓	↓	–	↓	↑ EE/↓ RQ	
DeLany *et al.* [146]	AKR/J	M	Mixture	0.25–1.0	6 weeks	↓	↓	↑	–		
Park *et al.* [36]	ICR	F	Mixture	0.5	8 weeks	–	↓	↑	↓		
Park *et al.* [18]	ICR	F	Mixture/c9t11/t10c12	0.25–0.5	4 weeks	↓ by t10c12	↓	↑	↓		
Tsuboyama *et al.* [65]	C57BL/6J	F	Mixture	1.0	5 months	–	↓	–			↓ TNF-α/↑ GLUT4
Park *et al.* [147]	ICR	M	Mixture	0.1	4 weeks	–	↓	↑			
Ohnuki *et al.* [53]	ddY	M	Mixture	0.25–1.0	4 and 8 weeks	↓	↓	–		↑ Oxygen consumption	
Peters *et al.* [73]	PPARα-KO	M	Mixture	0.5	4 weeks	↓	↓	↑			↑ CPT1/↑ UCP2
Park *et al.* [148]	ICR	F	Mixture	0.3	2 weeks	↓	–	–	↓		
Ntambi *et al.* [149]	ICR	F	Mixture	1.0	4 weeks	–	↓	↑			
Hayman *et al.* [150]	BALB/c	M	Mixture	0.1–2.0	4 weeks	↓	↓	↑		↔EE/↔VA/↔RER↔Oxygen consumption	
Warren *et al.* [151]	C57BL/6N	F	c9t11/t10c12	0.5	8 weeks	↓	↓	–			
Chardigny *et al.* [152]	ICR	F + M	c9t11/t10c12	1.0	6 weeks	–	↓	↑			
Terpstra *et al.* [153]	BALB/c	M	Mixture	0.5	6 weeks	↓	↓	↑	–	↑ EE	
Hargrave *et al.* [154]	MH/ML	M	Mixture	0.5	8 weeks	↓	↓	–	↓		
Park *et al.* [155]	ICR	M	t10c12	0.5	3 weeks	–	↓	↑			
Javadi *et al.* [156]	BALB/c	M	Mixture	0.5	3 and 12 weeks	↓	↓	↑			
Ohashi *et al.* [157]	C57BL, KK, KKAy	F	Mixture	0.5	4 weeks	↓	↓	–	–		
Javadi *et al.* [158]	BALB/c	M	Mixture	4.0	5 weeks	–	↓	–	–	↑ EE	
Park *et al.* [159]	ICR	F	Mixture	0.5	4 weeks	–	↓	↑	↓		
de Roos *et al.* [160]	ApoE KO	M	c9t11/t10c12	2.1	12 weeks	↓	↓	–	–		
Hargrave *et al.* [161]		M	Mixture	0.5	2 and 8 weeks	↓	↓	–	↓		
Winzell *et al.* [162]	C57BL/6J	F	Mixture	1.0	12 weeks	↓	↓	↑	–		
Bhattacharya *et al.* [163]	BALB/c	M	Mixture	0.5	14 weeks	↓	↓	–		↑ EE	
Viswanadha *et al.* [164]	CD-1	F	t10c12	0.15/0.3	6 weeks	–	↓	–			

Table 1 continued

References	Mouse		CLA supplementation			Results[e]				Muscle metabolism	
	Strain[a]	Gender[b]	Form[c]	Dosage (%)[d]	Duration	BW	BFM	LBM	Food intake	Energy expenditure[f]	Biomarkers[g]
Park *et al.* [44]	ICR	F + M	Mixture	0.5	4 weeks	↓	↓	↑	↓		
Rahman *et al.* [165]	C57BL/6J	F	Mixture	0.5	8 weeks	↓	↓	–	–		
Javadi *et al.* [166]	BALB/c	M	Mixture	0.5	4 weeks	↓	↓	–	–	↑ EE	
Park *et al.* [16]	ICR	M	Mixture	0.5	4 weeks		↓	↑			
Hur *et al.* [167]	N2KO	F	t10c12	0.5	12 weeks	↓	↓	–			
Andreoli *et al.* [168]	CF-1	M	Mixture	0.3	4 weeks	–	↓	–			
Halade *et al.* [97]	C57BL/6J	F	Mixture/c9t11/t10c12	0.5	6 months	↓	↓	↑	–		
Moon *et al.* [169]	ob/ob	M	Mixture	1.0	6 weeks	↓	↓	↑	–		
Halade *et al.* [20]	C57BL/6J	F	Mixture/c9t11/t10c12	0.5	6 months	↓	↓	↑	–		
Park *et al.* [55]	129Sv/J	F	Mixture	0.5	4 weeks	↓	↓	↑	↓	↑ EE/↓ RQ	↑ CPT-1/↑ UCP2/↑ GLUT 4
Parra *et al.* [170]	C57BL/6J	M	Mixture	3/10 mg/day	5 weeks	↓	↓	–	–		
Halade *et al.* [171]	C57BL/6J	F	Mixture/c9t11/t10c12	0.5	6 months	↓	↓	↑			
Park *et al.* [172]	ICR	M	Mixture/c9t11/t10c12	0.22/0.5	4 weeks	–	↓	↑	–		
Fedor *et al.* [173]	C57BL/6N	F	t10c12	0.5	4 weeks	↓	↓	–			
Scalerandi *et al.* [174]	CF-1	M	Mixture	1.0	4 weeks	↓	↓	–	–		

[a] *ApoE KO* apolipoprotein E knockout; *ddY* Deutschland, Denken, and Yoken; *MH* high metabolic rate; *ML* low metabolic rate; *N2KO* nescient helix-loop-helix 2 gene knockout; *PPARα-KO* peroxisome proliferator-activated receptor α knockout; *SENCAR* sensitive to carcinogenesis

[b] *F* female, *M* male

[c] Mixture, a mixed isomer of *cis*-9,*trans*-11 and *trans*-10,*cis*-12; c9t11, *cis*-9,*trans*-11 CLA isomer; t10c12,*trans*-10,*cis*-12 CLA isomer

[d] Dosage (%) denotes a designated weight percentage of CLA in diet

[e] *BW* body weight; *BFM* body fat mass; *LBM* lean body mass; – no change; ↑ increase; ↓ decrease. All changes are based on significant differences between or within groups as reported in publications

[f] *EE* energy expenditure; *RER* respiratory energy ratio; *RQ* respiratory quotient; *VA* voluntary activity

[g] *CPT* carnitine palmitoyltransferase, *GLUT4* glucose transporter type 4, *IL-6* interleukin 6, *TNF-α* tumor necrosis factor alpha, *UCP2* uncoupling protein 2, ↔ no change

Table 2 Summary of rat studies on conjugated linoleic acid (CLA) and body composition

References	Rat		CLA supplementation			Results[d]				Muscle metabolism	
	Strain	Gender[a]	Form[b]	Dosage (%)[c]	Duration	BW	BFM	LBM	Food intake	Energy expenditure	Biomarkers[e]
Stangl *et al.* [22]	SD	M	Mixture	3.0	7 weeks	↓	↓	↑			
Azain *et al.* [175]	SD	F	Mixture	0.25/0.5	1, 5 and 7 weeks	–	↓	–	–		
Sisk *et al.* [176]	Zucker	M	Mixture	0.5	5 and 8 weeks	–	–	–			
Kim *et al.* [177]	SD	M	Mixture	0.5-1.0	9 weeks	–	–	–			
Yamasaki *et al.* [178]	SD	M	Mixture	1.5	3 weeks	–	↓	–			
Henriksen *et al.* [179]	Zucker	F	Mixture/ c9t11/ t10c12	0.42 g/day	3 weeks	↓ by Mixture and t10c12	↓ by t10c12	–			↓ protein carbonyl/ ↓ intramuscular TAG/ ↑ glucose uptake by Mixture and t10c12
Sanders *et al.* [180]	Zucker	F	Mixture/ c9t11/ t10c12	0.42 g/day	3 weeks	↓ by Mixture and t10c12	–	–			
Botelho *et al.* [181]	Wistar	M	Mixture	2.0	6 weeks	–	↓	↑	↑		
Ogborn *et al.* [182]	Han: SPRD-cy	F + M	Mixture	1.0/2.0	12 weeks	–	↓	–			
Roy *et al.* [183]	SD	M	Mixture	1.0	8 weeks	–	–	–			
DeGuire *et al.* [184]	SD	F + M	Mixture	1.0	16 weeks	–	–	–			
de Almeida *et al.* [185]	Wistar	M	Mixture	1.5	9 weeks	–	–	–			

[a] *F* female, *M* male

[b] Mixture, a mixed isomer of *cis*-9,*trans*-11 and *trans*-10,*cis*-12; c9t11, *cis*-9,*trans*-11 CLA isomer; t10c12,*trans*-10,*cis*-12 CLA isomer

[c] Dosage (%) denotes a designated weight percentage of CLA in diet

[d] *BW* body weight, *BFM* body fat mass, *LBM* lean body mass; – no change, ↑ increase; ↓ decrease. All changes are based on significant differences between or within groups as reported in publications

[e] *TAG* triglyceride

have suggested that the temporary reduction in food intake as seen with a CLA-containing diet may be due to its palatability when CLA is used as a free fatty acid. Moreover, in a study using a pair-feeding comparison, changes in body composition occurring with CLA were shown to be independent of reduced food intake [44], and human clinical trials showed no effect of CLA supplementation on food intake [29, 30, 45–49]. These human studies all used self-reported food intake methods, which calls into question their validity [50]. Nevertheless, despite the lack of conclusive evidence regarding the relationship between CLA and dietary intake in humans, it is unlikely that the reduction in food intake is the main mechanism of action for the change in body composition seen with CLA.

Enhanced energy expenditure is one key to controlling body composition. Several animal studies have suggested that CLA increases overall energy expended [43, 51–58]. In clinical trials, CLA supplementation was shown to

Table 3 Summary of human studies on conjugated linoleic acid (CLA) and body composition

References	Subject		CLA supplementation			Results[d]			Energy expenditure[e]	Other comments
	Characteristic	Gender[a]	Form[b]	Dose (g/day)	Duration	BW	BFM	LBM		
Berven *et al.* [186]	Overweight/obese	F + M	Mixture	3.4	12 weeks	↓	–	–		
Blankson *et al.* [114]	Overweight/obese	F + M	Mixture	1.7/3.5/5.1/6.8	6 and 12 weeks	–	↓ 1.7, 3.4 and 6.8 at 12 weeks	↑ 6.8 at 12 weeks		
Zambell *et al.* [63]	Normal	F	Mixture	2.5	9 weeks	–	–	–	↔ RMR/↔ REM	
Kreider *et al.* [115]	Normal/overweight	M	Mixture	6.0	4 weeks	–	–	–		
Riserus *et al.* [187]	Obese	M	Mixture/t10c12	3.4	12 weeks	↓ by t10c12	↓ by Mixture and t10c12	–		Subjects with metabolic syndrome
Kamphuis *et al.* [28]	Overweight	F + M	Mixture	1.8/3.6	13 weeks	–	↓	↑	↑ RMR	Weight regain
Gaullier *et al.* [29]	Overweight	F + M	Mixture (TAG/Free form)	3.6/3.4	1 year	↓	↓	↑	↑ EE	Free-form increased LBM/↓ food intake
Malpuech-Burugere *et al.* [47]	Overweight	F + M	TAG of c9t11 and t10c12	1.5/3.0	18 weeks	–	–	–		↓ Food intake
Riserus *et al.* [188]	Obese	M	TAG of c9t11	3.0	12 weeks	↑	–	–		
Gaullier *et al.* [45]	Overweight	F + M	Mixture (TAG/Free form)	3.6/3.4	2 year	↓	↓	–		1-year extension open study/↓ food intake
Colakoglu *et al.* [116]	Normal	F	Mixture	3.6	6 weeks	↓	↓	↑		
Larsen *et al.* [189]	Overweight/obese	F + M	Mixture	3.4	1 year	–	–	–		Weight regain/hypocaloric diet
Pinkoski *et al.* [61]	Unknown	F + M	Mixture	5.0	7 weeks		↓	↑	↔ RMR	↓ Protein degradation
Gaullier *et al.* [30]	Overweight/obese	F + M	Mixture	3.4	6 months	–	↓	↑		↔ Calorie intake
Lambert *et al.* [62]	Normal/overweight	F + M	Mixture	2.6	12 weeks	–	–	–	↔ RMR	↔ Appetite
Laso *et al.* [190]	Overweight/obese	F + M	Mixture	3.0	12 weeks	–	↓	–		
Nazare *et al.* [59]	Normal/overweight	F + M	Mixture (TAG)	2.8	14 weeks	–	–	–	↑ RMR	↓ Food intake
Steck *et al.* [33]	Obese	F + M	Mixture	3.2/6.4	12 weeks	–	–	↑	↔ RMR/↔ RQ	
Tarnopolsky *et al.* [117]	Normal/overweight	F + M	Mixture	5.4 + 5 g creatine mono-hydrate	6 months	–	↓	↑		Co-supplementation/aging study model
Watras *et al.* [48]	Overweight	F + M	Mixture	3.2	6 months	↓	↓	–	↑ RMR	↔ Energy intake
Diaz *et al.* [118]	Overweight/obese	F	Mixture	1.8 + 0.4 mg creatine picol-inate	12 weeks	–	–	–		Co-supplementation/premenopausal
Park *et al.* [191]	Overweight/obese	F + M	Mixture	2.4	8 weeks	↓	–	–		↓ Food intake
Sneddon *et al.* [34]	Normal/obese	M	Mixture	2.3 + 1.3 g ω-3 fatty acid	12 weeks	↑	–	↑		Co-supplementation/crossover design

Table 3 continued

References	Subject		CLA supplementation			Results[d]			Energy expenditure[e]	Other comments
	Characteristic	Gender[a]	Form[b]	Dose (g/day)	Duration	BW	BFM	LBM		
Norris *et al*. [192]	Obese	F	Mixture	6.4	16 weeks	↓	↓	–		Type 2 diabetes/postmenopausal
Raff *et al*. [31]	Normal/overweight/obese	F	Mixture/c9t11	5.5/4.7	16 weeks	–	↓ by Mixture	↑ by Mixture		Postmenopausal
Cornish *et al*. [46]	Obese	F + M	Mixture	4.3 + 9 g creatine monohydrate + 36 g whey protein	5 weeks	–	–	↑		↔ Energy intake
Racine *et al*. [32]	Overweight/obese	F + M	Mixture (TAG)	2.4	7 months	↓	↓	↑		Childhood model
Joseph *et al*. [193]	Overweight/obese	M	Mixture/c9t11	2.8/2.7	8 weeks	–	–	–		Crossover design
Chen *et al*. [119]	Overweight/obese	F + M	Mixture	1.7	12 weeks	↓	↓	–		
Macaluso *et al*. [126]	Normal/overweight	M	Mixture	4.8	3 weeks	–	–	–		Crossover design/serum testosterone ↑
Lopez-Plaza *et al*. [194]	Overweight	F + M	Mixture	3.0	24 weeks	↓	↓	–		
Shadman *et al*. [195]	Overweight	F + M	Mixture	2.4 + 100 IU/day vitamin E	8 weeks	–	–	–		Co-supplementation/type 2 diabetes
Ormsbee *et al*. [196]	Overweight/obese	F + M	Mixture	CLA + Green tea + BCAA[c]	8 weeks	↓	–	–		Co-supplementation

[a] *F* Female, *M* male

[b] Mixture, a mixed isomer of *cis*-9,*trans*-11 and *trans*-10,*cis*-12; c9t11, *cis*-9,*trans*-11 CLA isomer; t10c12,*trans*-10,*cis*-12 CLA isomer; TAG, triglyceride form; Free form, free fatty acid form

[c] Green tea, standardized for 45 % epigallocatechin gallate and 90 % polyphenol; BCAA, branched-chain amino acid

[d] *BW* body weight, *BFM* body fat mass, *LBM* lean body mass; – no change, ↑ increase, ↓ decrease. All changes are based on significant differences between or within groups as reported in publications

[e] *EE* energy expenditure, *RER* respiratory energy ratio, *RMR* resting metabolic rate, *RQ* respiratory quotient, ↔ no change

increase BMR (as resting metabolic rate, RMR) [28, 48, 59, 60], although other studies found no influence of CLA on BMR, regardless of changes in body composition [33, 61–63].

As part of the increased expenditure of energy, CLA supplementation may increase thermogenesis, as evidenced by the upregulation of uncoupling proteins (UCPs) expressed in various tissues, such as the adipose, liver, and the skeletal muscle in mice and rats [38, 40, 55, 56, 64–66]. UCP1 through UCP5 are mitochondrial proteins involved in the combustion of stored or excess energy into heat. They are expressed in distinct tissues in the body, and are responsible for adaptive thermogenesis. Thus, an increase in UCPs by CLA suggests that CLA may increase energy expenditure by enhancing thermogenesis [67]. Likewise, physical activity also contributes to the overall expenditure of energy. Studies in rodents have reported that CLA supplementation increased energy expenditure in part by increasing the level of physical activity [43, 56, 68], although human studies are inconsistent in this regard [59, 61, 69].

In addition, fatty acid β-oxidation may contribute to reducing body fat mass by using fat as an energy source, rather than storing it in the body. Increased fat oxidation in CLA-fed animals has been reported, as measured either by reduced respiratory quotient or by increased activity and/or the expression of carnitine palmitoyltransferase 1 (CPT-1) in the skeletal muscle [12, 21, 41, 55, 56, 68, 70–74]. Intriguingly, Close *et al*. [60] reported that human subjects who received supplements with 4 g of CLA mixture for 6 months had significantly increased fat oxidation and energy expenditure during sleep. In another study, CLA was found to potentiate adipocyte apoptosis, reduce fat uptake, and/or modulate adipokine production, all of which collectively contributed to the effective reduction of fat accumulation [17]. At the same time, CLA increased lean mass, which is an important observation, suggesting that CLA targets skeletal muscle metabolism. The potential effects of CLA on skeletal muscle metabolism, however, have been less investigated.

CLA and Skeletal Muscle Metabolism

Skeletal muscle typically accounts for nearly 40 % of total body mass, and acts as a significant regulator in overall energy metabolism [75]. Muscle metabolism is a term used to describe the complex biochemical reactions associated with skeletal muscle function and development.

Overview of Muscle Energy Metabolism

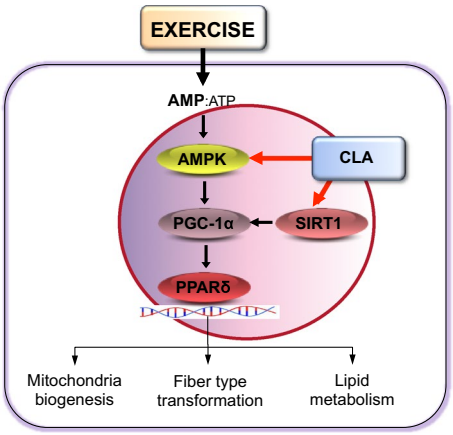
The process of energy production for skeletal muscle is tightly regulated by the type, intensity, and duration of muscle exercise [76, 77]. Glycolysis is the catabolic pathway for glucose in the cytosol under both anaerobic (absence of oxygen) and aerobic (presence of oxygen) conditions. Aerobic glycolysis is an efficient means of producing adenosine triphosphate (ATP) through mitochondrial oxidative phosphorylation, while anaerobic glycolysis produces an energy supply with a much lower yield (36–38 ATPs produced by aerobic glycolysis vs. 2 ATPs by anaerobic glycolysis). During high-intensity exercise, anaerobic metabolic pathways are important, as aerobic metabolism alone may not be adequate to meet energy demands, especially when there is insufficient oxygen supply [78–80]. In contrast, low-intensity endurance exercise (requiring less than 60 % of maximal oxygen uptake) such as jogging and swimming consumes glucose and fatty acids as the primary energy sources during the first hour, and then relies on stored intramuscular and adipose tissue triglycerides for energy [81]. Thus it is believed that prolonged endurance exercise is the more efficient way to consume stored body fat.

Adaptive Responses of Skeletal Muscle

The skeletal muscle tissue also demonstrates metabolic plasticity in response to altered external and internal conditions, such as nutrient deprivation during fasting or calorie restriction and contractile activity including exercise [82]. One of the adaptive responses of the muscle is the ability to change the fiber type to meet energy demands. Muscle fiber in humans is composed of three myosin heavy chain (MHC) isoforms: MHC I, MHC IIa, and MHC IIx/d or IIb. MHC I are slow-twitch type I fibers, which have greater mitochondrial content, oxidative capacity, and resistance to fatigue, using fatty acids as a main energy source. Fast-twitch type II fibers (especially type IIb) are classified as glycolytic fibers, since they use glucose and phosphocreatine as primary energy sources. Type IIa is an intermediate type between type I and type IIb [83]. In response to exercise, the skeletal muscle remodels its fiber type between oxidative slow-twitch and glycolytic fast-twitch [84] in correlation with the contractile properties and the physiological and metabolic characteristics [85]. For example, an endurance exercise triggers fiber type remodeling from glycolytic fast-twitch to oxidative slow-twitch [84]. These adaptations in the skeletal muscle are accompanied by an increase in mitochondrial biogenesis, with the alteration of mitochondrial volume (content per gram of tissue) and composition (protein-to-lipid ratio in the inner mitochondrial membrane) [86].

Molecular Responses of Skeletal Muscle Metabolism

A number of regulators participate in the above-described adaptive responses in skeletal muscle. Among them,



Scheme 1 Proposed mechanism of CLA on muscle metabolism. *AMPK* AMP-activated protein kinase, *CLA* conjugated linoleic acid, *SIRT1* silent information regulator two protein 1, *PGC-1α* peroxisome proliferator-activated receptor γ coactivator 1α, *PPARδ* peroxisome proliferator-activated receptor δ (Used with permission of UMass Amherst)

AMP-activated protein kinase (AMPK) is the prime initial sensor of fuel and energy status in the skeletal muscle (Scheme 1) [87]. An increase in intracellular AMP concentration causes a shift to an increased AMP/ATP ratio, and AMPK is then activated to provide the needed energy in the cell. An activated AMPK deactivates acetyl-CoA carboxylase (ACC) by phosphorylation, inhibits the synthesis of malonyl-CoA from two acetyl-CoAs, and results in the activation of carnitine palmitoyltransferase 1 (CPT1), a rate-limiting enzyme for fatty acid β-oxidation in mitochondria. AMPK also induces metabolic changes including an increase in glucose uptake by the induction of glucose transporter type 4 (GLUT4), translocation in the skeletal muscle, and a decrease in the rate of glycogen synthesis through the phosphorylation of glycogen synthase [82]. Similar to AMPK, sirtuin 1 (SIRT1, a conserved nicotinamide adenine dinucleotide $[NAD]^+$-dependent deacetylase) acts as a sensor of metabolic stimuli (such as stress, starvation, or calorie restriction) [88]. SIRT1 also regulates several transcriptional factors (including protein 53, forkhead box O, and nuclear factor κ-light-chain-enhancer of activated B cells, NFκB), and is known to be involved in longevity [88]. Both AMPK and SIRT1 may coherently mediate the response at the cellular level to the metabolic stimuli in the skeletal muscle [89].

Peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), a downstream target of AMPK and SIRT1, regulates several downstream transcription factors, including peroxisome proliferator-activated receptor δ (PPARδ), nuclear respiratory factor-1 and -2 (NRF), estrogen-related receptor α (ERRα), and myocyte enhancer factor 2 (MEF2). These factors are important in initiating mitochondrial biogenesis and inducing fiber type transformation in the skeletal muscle [90, 91]. Further support for the significance of PGC-1α was provided in a study reporting that ectopically expressing PGC-1α in the skeletal muscle of transgenic mice induced the muscle fiber conversion of glycolytic fast-twitch type II fibers into oxidative slow-twitch type I fibers [92]. In a similar manner, the overexpression of PPARδ (a downstream regulator of PGC-1α) resulted in the development of slow-twitch type I fibers in skeletal muscle [93, 94]. The signaling cascade AMPK to PPARδ via PGC-1α is an important metabolic pathway involved in adaptive metabolism in the skeletal muscle. As such, we have focused primarily on this pathway to uncover the potential mechanism of CLA in skeletal muscle metabolism.

Overall Effects of CLA on Skeletal Muscle Metabolism

Previous studies using mouse models have clearly suggested that CLA is associated with a significant quantitative increase in lean mass [12, 95]. In addition, CLA supplementation up-regulates CPT1 and UCP2 from the skeletal muscle, suggesting that an overall increase in energy expenditure and fatty acid oxidation with CLA may contribute to the reduction in fat accumulation [52, 56, 95, 96]. CLA has also been reported to prevent age-associated skeletal muscle loss in aged rodents [19, 97]. The preventive role of CLA in muscle is further supported by our results in Fig. 1 with animals known to develop inactivity-induced obesity with muscle dystrophy. When a cognate of CLA (conjugated nonadecadienoic acid, known to have biological effects similar to those of CLA) was given to these animals, we observed an increase in voluntary activity and a reduction in body fat, as well as an increase in muscle size, suggesting that this treatment may have prevented muscle dystrophy typically associated with these animals [56, 98].

Effects of CLA on Adaptive Muscle Responses

There is currently limited evidence demonstrating the role of CLA in skeletal muscle metabolism [19, 21, 66, 99–102]. Supplementation of 1.2–2.0 % CLA in the diet of pigs was found to significantly increase expression levels of oxidative slow-twitch type I fiber, but did not increase the expression of glycolytic fast-twitch type IIb and IIx fibers in the pig's skeletal muscle [103]. However, fiber type changes are dependent on the growth phase in pigs [104]. Similarly, Parra *et al.* [100] observed no CLA effect on PPARδ and muscle fiber change in mice. Given these limited studies, it cannot be conclusively stated that CLA promotes muscle fiber type transformation. However, along with the observation that CLA is linked to improved maximum endurance capacity in mice, it is highly likely that

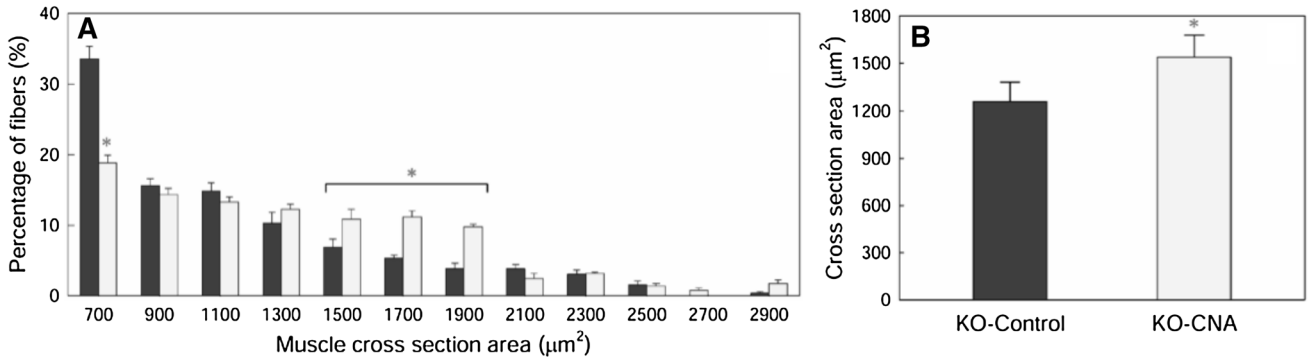


Fig. 1 A cognate of CLA, conjugated nonadecadienoic acid (CNA), significantly prevented muscle dystrophy in animals with inactivity-induced obesity. **a** The data show that CNA supplementation (*light gray bars*) resulted in a reduced number of smaller muscles (less than 700 μm) and increased number of medium-sized muscles (between 1500 and 2100 μm) compared to controls (*black bars*). **b** CNA-fed animals had significantly increased average muscle size compared to Nhlh-2 knockout controls. *Significantly different at $P < 0.05$. Six-week-old female Nhlh-2 KO mice were fed either a control or CNA-containing diet (0.1 % w/w of diet) for 8 weeks [semi-purified powder diet, TD07518 (Teklad; Harlan Laboratories/Envigo, Madison, WI, USA) with "vitamin-free" tested casein to avoid the naturally occurring CLA in casein was used]. The diet consisted of an AIN-93-based diet with 20 % fat total as soybean oil. The thigh muscle, vastus lateralis, was frozen in liquid nitrogen, and frozen muscles were cut into 10-μm section using a Cryotome. The sections were stained with hematoxylin and eosin in order to visualize the muscle, and muscle size was measured (>500 fibers) with ImageJ software (NIH). Numbers are mean ± S. E ($n = 3$)

CLA influences muscle fiber type transformation [21, 68, 105, 106]. The effect of CLA on physical activity is further discussed below.

Effects of CLA on Molecular Responses of Muscle Metabolism

Several studies have reported the effects of CLA on the biochemical alteration of several molecular markers of muscle metabolism [19, 21, 66, 99–102]. CLA treatment was shown to activate AMPK in murine skeletal muscle cells [107–110], which negatively regulated ACC and enhanced fatty acid β-oxidation [107, 110]. One study reported that the *cis-9,trans-11* CLA isomer activated AMPK at lower concentrations (~50 μM), while the *trans-10,cis-12* isomer gradually activated AMPK in a dose-dependent manner up to 120 μM, and then plateaued [108]. However, the effect of CLA on SIRT1 activity in the skeletal muscle is currently not known [109].

CLA treatment did not affect the activity of PGC-1α, a primary regulator in mitochondrial biogenesis, even when the mitochondrial content in the human skeletal muscle cells was increased by CLA [101]. Similarly, CLA-fed mice and rats demonstrated no significant differences in PGC-1α compared to control groups [66, 100]. On the other hand, CLA treatment significantly up-regulated PGC-1α in murine skeletal muscle cells [109], supporting the contention that CLA supplementation significantly up-regulates molecular biomarkers such as succinate dehydrogenase, cytochrome c oxidase, superoxide dismutase 2, catalase, and glutathione peroxidase in the skeletal muscle, which is related to increased ATP production and thermogenesis via improved oxidative phosphorylation and anti-oxidative capacity in the rodent models [19, 66]. These results suggest that further confirmation is needed as to whether CLA treatment is associated with mitochondrial biogenesis through PGC-1α. Thus, further investigation is required, particularly in humans, for a better understanding of the correlation between CLA supplementation and muscle fiber type transformation. In addition, CLA—in particular, *trans-10,cis-12*—increased PPARδ expression in murine muscle cells and mice [21, 102]. While these results suggest that CLA may target muscle metabolism, no mechanistic studies have been completed to determine whether CLA directly or indirectly influences any of these molecular targets.

Effect of CLA on Physical Activity

Animal studies using CLA and exercise are summarized in Table 4. Studies using mice showed consistent effects of reduced body fat or increased lean mass. Moreover, there was a significant improvement in the exercise outcome with CLA treatment (Table 4) [21, 68, 105, 106, 111]. Specifically, Kim *et al.* [21] reported that the *trans-10,cis-12* isomer was responsible for this effect, but not the *cis-9,trans-11* isomer. This is consistent with the role of the *trans-10,cis-12* isomer as the active isomer in body fat reduction [18]. In contrast, studies in rats observed no additional or synergistic effects of CLA treatment and exercise training on endurance capacity and lean body mass [43, 112]. This discrepancy was previously recognized as

Table 4 Summary of studies using conjugated linoleic acid (CLA) and exercise regimen in animals

References	Animal		CLA supplementation			Results[d]			Exercise type	Muscle metabolism		Exercise outcome
	Strain	Gender[a]	Form[b]	Dosage[c]	Duration	BW	BFM	LBM		Energy expenditure[e]	Biomarkers[f]	
Mizunoya *et al.* [68]	BALB/c Mice	M	Mixture	0.5 %	1 week	–	↓	–	Endurance (swimming and running)	↓ RER ↑ Fat oxidation	↑ LPL	↑
Bhattacharya *et al.* [57]	BALB/c Mice	M	Mixture	0.4 %	14 weeks	↓	↓	↑	Endurance (running)	↔ EE		
Di Felice *et al.* [197]	ICR Mice	M	Mixture	0.425 mg/day	6 weeks	–		↑	Endurance (running)		↑ Muscle hypertrophy	
Banu *et al.* [198]	C57BL/6 Mice	F	Mixture	0.5 %	10 weeks	↓	↓	↑	Endurance (running)			
Zhang *et al.* [199]	ICR Mice	M	Mixture	0.5 %	18 weeks	↓			Endurance (swimming)			↔
Kim *et al.* [105]	BALB/c Mice	M	Mixture	1.0 %	10 weeks	↓			Endurance (running)			↑
Kim *et al.* [21]	129 Sv/J Mice	M	c9t11/t10c12	0.5 %	6 weeks	↓	↓	↑	Endurance (running)		↑ CPT1/↑ UCP2/↑ PPARδ	↑ by t10c12
Hur *et al.* [111]	ICR Mice	F	Mixture	1.0 %	6 weeks	↓	↓		Endurance (running)			↑
Barone *et al.* [106]	BALB/c Mice	M	Mixture	0.5 %	6 weeks	↓		↑	Endurance (running)		↑ Testosterone	↑
Shen *et al.* [200]	129 Sv/J Mice	M	t10c12	0.1 %	7 weeks	↓	↓		Endurance (running)			
Mirand *et al.* [201]	Wistar Rats	M	Mixture/c9t11/t10c12	1.0 %	6 weeks	–	–	–	Endurance (running)			
Faulconnier *et al.* [202]	Wistar Rats	M	Mixture/c9t11/t10c12	1.0 %	6 weeks	–	↓		Endurance (running)			
Mirand *et al.* [43]	Wistar Rats	M	Mixture/c9t11/t10c12	1.0 %	6 weeks	–		↑ by Mixture	Endurance (running)			
Salgado *et al.* [112]	Wistar Rats	F + M	Mixture	0.5 %	10 weeks	↓	↓	↑	Endurance (swimming)			

[a] *F* female, *M* male

[b] Mixture, a mixed isomer of *cis*-9,*trans*-11 and *trans*-10,*cis*-12; c9t11, *cis*-9,*trans*-11 CLA isomer; t10c12,*trans*-10,*cis*-12 CLA isomer

[c] Dosage (%) denotes a designated weight percentage of CLA in diet

[d] *BW* body weight, *BFM* body fat mass, *LBM* lean body mass; – no change, ↑ increase, ↓ decrease. All changes are based on significant differences between or within groups as reported in publications

[e] *EE* energy expenditure, *RER* respiratory energy ratio, ↔ no change

[f] *CPT1* carnitine palmitoyltransferase 1, *LPL* Lipoprotein lipase, *PPARδ* peroxisome proliferator-activated receptor δ, *UCP2* uncoupling protein 2

a consequence of the greater sensitivity of mice than of rats to CLA, partly due to differences in the administered CLA dose on a weight basis and/or differences in the physiology of animals (in particular, male rats continuously gain weight, and no significant effects of CLA have been reported for body fat) [113].

There are currently 17 CLA human intervention studies reporting on CLA with exercise, as summarized in Table 5.

Among them, ten studies tested exercise outcomes [46, 61, 114–122]. Overall, the effect of CLA supplementation on exercise outcome varied across studies; six reported positive results [46, 61, 114, 116, 117, 120], while others reported no difference [115, 118, 119, 121, 122]. Four clinical trials evaluated the effect of CLA supplementation on physical activity, without a regular exercise regime [30, 48, 123, 124]. Among them, one study reported improved physical activity with CLA treatment over a period of 3 months [123]. In general, the studies were relatively short-term in nature (with the exception of two, they were less than 12 weeks in length), and thus no conclusion can be drawn as to whether the lack of effect was due to the limited supplementation periods or the ineffectiveness of CLA.

Four studies in humans evaluated the effects of co-supplementation of CLA with other supplements, such as creatine monohydrate, chromium picolinate, whey protein, or amino acids, along with exercise training [46, 117, 118, 125]. Two of these studies used CLA and creatine monohydrate for short- (5 weeks) or long-term (6 months) durations, accompanied by resistance training, and reported increased lean body mass and improved strength compared to the control group [46, 117].

Interestingly, Macaluso *et al.* [126] conducted a clinical trial to investigate the effect of CLA with resistance training on serum testosterone levels. The authors reported significantly increased serum testosterone and resistance exercise capability with CLA supplementation, with no significant change in body weight, fat mass, or lean body mass. Others have reported that testosterone can improve mitochondrial biogenesis and total energy expenditure, and that CLA supplementation was found to promote endurance capacity in trained mice via the upregulation of testosterone biosynthesis [106, 127]. Thus, it is possible that CLA improves exercise outcome by modulating testosterone; however, the Macaluso *et al.* [126] study may have been too short to have observed changes in body composition due to CLA. Generally, indications are that CLA may influence muscle metabolism, but mechanistic studies are currently lacking.

Potential Health Concerns of CLA

Based on the results of animal and human studies, four aspects of CLA supplementation are of concern: insulin sensitivity, oxidative stress, maternal milk fat, and liver function. These topics have been previously reviewed in detail [5, 14, 15]. Among these potential health concerns, the effects of CLA on glucose metabolism may affect the potential role of CLA in skeletal muscle metabolism, and effects are inconsistent in both animal and human studies. However, evidence suggests that the long-term use of CLA, particularly as a mixture of the two main isomers, will likely have no adverse influence on glucose metabolism [5, 45, 128].

Other health concerns associated with CLA do not directly involve the skeletal muscle metabolism, although this aspect is important in understanding the health impact of CLA. Reports of human studies have consistently linked CLA supplements to increased oxidative markers, particularly isoprostanes, but not to other biomarkers [5, 129, 130]. It has been suggested that CLA itself might be metabolized to structurally similar isoprostanes that cannot be distinguished from the isoprostanes used as oxidative markers [131, 132].

CLA is known to reduce body fat, and CLA supplementation has been reported to significantly reduce milk fat, particularly in cows [133, 134]. A limited number of human studies have reported none or minimal change in milk fat content after short-term CLA supplementation (less than 5 days) [135–137], and in light of the primary difference in milk fat origin between ruminants and humans, CLA is expected to have minimal effects on human milk fat [133, 134]. The long-term effects of CLA on human milk fat have yet to be determined.

In animal studies, there have been consistent observations of an enlarged liver with CLA feeding, but minimal changes have been reported in human studies [8, 65, 138–142]. While it is likely that the effect of CLA on the enlarged liver is specific to rodents, three human cases of hepatitis have been associated with CLA [143–145]. Thus, close monitoring of CLA supplementation with regard to the health of the liver will be important, particularly with long-term use.

Conclusion

To date, most mechanistic studies of the effects of CLA on body composition have focused on lipid metabolism in the adipose tissue. At the same time, a growing number of studies have highlighted the importance of CLA with respect to skeletal muscle metabolism, with effects including increased energy expenditure and enhanced physical activity. However, mechanistic studies investigating the mechanism by which CLA modulates skeletal muscle metabolism are very preliminary, and further investigation of the mechanistic effects of CLA on the skeletal muscle metabolism, including mitochondrial biogenesis and muscle fiber type transformation, is needed. We expect that knowledge of the effect

Table 5 Summary of human studies determining effects of conjugated linoleic acid (CLA) and exercise

References	Subject		CLA supplementation			Results[d]			Exercise type	Muscle metabolism		Exercise outcome
	Characteristic	Gender[a]	Form[b]	Dosage[c]	Duration	BW	BFM	LBM		Energy expenditure[e]	Biomarkers[f]	
Blankson *et al.* [114]	Overweight/obese	F + M	Mixture	1.7/3.5/5.1/6.8	6 and 12 weeks	–	↓ 1.7, 3.4 and 6.8 at 12 week	↑ 6.8 at 12 week	Standardized training			↑
Thom *et al.* [203]	Normal	F + M	Mixture	1.8	12 weeks	–	↓		Strenuous			
Kreider *et al.* [115]	Normal/overweight	M	Mixture	6.0	4 weeks	–	–	–	Resistance			↔
Loeffelholz *et al.* 2003	Overweight	F + M	Mixture	3.8	6 months	–	↓		Resistance			
Colakoglu *et al.* [116]	Normal	F	Mixture	3.6	6 weeks	↓	↓	↑	Endurance			↑
Pinkoski *et al.* [61]	Unknown	F + M	Mixture	5.0	7 weeks		↓	↑	Resistance	↔ RMR		↑
Adams *et al.* [204]	Overweight/obese	M	Mixture	3.2	4 weeks	–			Resistance			
Nazare *et al.* [59]	Normal/overweight	F + M	Mixture (TAG)	2.8	14 weeks	–	–	–	Regular training	↑ RMR		
Tarnopolsky *et al.* [117]	Normal/overweight	F + M	Mixture	5.4 + 5 g creatine monohydrate	6 months	–	↓	↑	Resistance			↑
Diaz *et al.* [118]	Overweight/obese	F	Mixture	1.8 + 0.4 mg chromium picolinate	12 weeks	–	–	–	Endurance			↔
Cornish *et al.* [46]	Obese	F + M	Mixture	4.3 + 9 g creatine monohydrate + 36 g whey protein	5 weeks	–	–	↑	Resistance			↑
Michishita *et al.* [125]	Normal/overweight	F + M	Mixture	1.6 + 1.52 g amino acids	12 weeks	–	–		Resistance			
Chen *et al.* [119]	Overweight/obese	F + M	Mixture	1.7	12 weeks	↓	↓	–	Resistance			
Macaluso *et al.* [126]	Normal/overweight	M	Mixture	4.8	3 weeks	–	–	–	Resistance		↑ Testosterone in serum	↔
Bulut *et al.* [205]	Overweight	M	Mixture	3.0	4 weeks	–	–	–	Endurance			

Table 5 continued

References	Subject		CLA supplementation			Results[d]			Exercise type	Muscle metabolism		Exercise outcome
	Characteristic	Gender[a]	Form[b]	Dosage[c]	Duration	BW	BFM	LBM		Energy expenditure[e]	Biomarkers[f]	
Jenkins *et al.* [121, 122]	Normal/overweight	M	Mixture	5.63	6 weeks				Endurance	↔ PWC_{FT} ↔ VO_2 max ↔ GET ↔ RCP		↔
Tsao *et al.* [69]	Normal	M	Mixture	3.8	8 weeks	–			Endurance	↔ RMR	↑ Glycogen resynthesis/ ↑ GLUT4	

[a] *F* female, *M* male

[b] Mixture, a mixed isomer of *cis*-9,*trans*-11 and *trans*-10,*cis*-12; c9t11, *cis*-9,*trans*-11 CLA isomer; t10c12,*trans*-10,*cis*-12 CLA isomer

[c] Dosage (%) denotes a designated weight percentage of CLA in diet

[d] *BW* body weight, *BFM* body fat mass, *LBM* lean body mass; – no change, ↑ increase, ↓ decrease. All changes are based on significant differences between or within groups as reported in publications

[e] *GET* gas exchange threshold, PWC_{FT} physical working capacity at the fatigue threshold, *RCP* respiratory compensation point, *RMR* resting metabolic rate, VO_2 *max* maximal oxygen uptake, ↔ no change

[f] *GLUT4* glucose transporter type 4

of CLA on muscle metabolism will help to elucidate the preventive effects of CLA on obesity, along with current knowledge of its effects on adipose tissue. This knowledge will also support the potential application of CLA in the prevention of age-associated muscle loss, such as sarcopenia.

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