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Conjugated Linoleic Acid: Potential Health Benefits as a Functional Food Ingredient

Jun Ho Kim,[1] Yoo Kim,[2] Young Jun Kim,[1] and Yeonhwa Park[2]

[1]Department of Food and Biotechnology, Korea University, Sejong 339-700, Republic of Korea

[2]Department of Food Science, University of Massachusetts, Amherst, Massachusetts 01003; email: ypark@foodsci.umass.edu

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Abstract

Conjugated linoleic acid (CLA) has drawn significant attention since the 1980s for its various biological activities. CLA consists mainly of two isomers, *cis*-9,*trans*-11 and *trans*-10,*cis*-12, and the mixture of these two (CLA mix or 50:50) has been approved for food as GRAS (generally recognized as safe) in the United States since 2008. Along with its original discovery as an anticancer component, CLA has been shown to prevent the development of atherosclerosis, reduce body fat while improving lean body mass, and modulate immune and/or inflammatory responses. This review summarizes the clinical trials involving CLA since 2012; additional uses of CLA for age-associated health issues are discussed; and CLA's potential health concerns, including glucose homeostasis, oxidative stress, hepatic steatosis, and milk-fat depression, are examined. With ongoing applications to food products, CLA consumption is expected to rise and close monitoring of not only its efficacy but also its known and unknown consequences are required to ensure proper applications of CLA.

INTRODUCTION

Along with scientific advances linking health and diet, there is great public interest in functional foods, particularly functional lipids. Among them, conjugated linoleic acid (CLA) has drawn significant scientific attention in the past few decades. CLA is the name for an 18-carbon polyunsaturated fatty acid with two conjugated double bonds. Interest in CLA began with the first report of its anticancer biological function in 1987 and expanded when its antiobesity properties were discovered in 1997 (Ha et al. 1987, Park et al. 1997). Currently, there are more than 3,900 publications (Web of Science, May 19, 2015), with over 90,000 citations, dealing with CLA, reflecting the high amount of scientific interest in this compound.

The earliest report of CLA in history can be traced back to 1933 when milk samples from summer were found to have a greater light absorption at 230 nm compared to milk samples from winter (Parodi 1999). This can be inferred as the presence of conjugated double bonds from CLA. It was later proved that milk from pasture-fed cows (summer) contains more CLA than milk from grain-fed cows (winter) (Parodi 1999). However, it took until 1987 to uncover the biological function of CLA, when Dr. Pariza's group at the University of Wisconsin-Madison discovered that the anticancer property of beef extract was due to CLA (Ha et al. 1987) and then confirmed its anticancer efficacy. When CLA's antiobesity effect was reported in 1997 (Park et al. 1997), there was another explosion of interest in CLA research. This paper reviews the biological effects of CLA, including potential health concerns, with particular emphasis on publications involving humans since 2012, and also explores other potential applications of CLA.

ORIGINS OF CONJUGATED LINOLEIC ACID

Although CLA discovered from natural sources is mainly the *cis*-9,*trans*-11 isomer, it is important to point out that CLA is a mixture of a number of geometric and positional isomers of octadecadienoic acids (Chin et al. 1992, Kramer et al. 1998). The earliest publication that identified the *cis*-9,*trans*-11 isomer was in 1966, when Kepler et al. (1966) reported biohydrogenation by rumen bacteria converted polyunsaturated linoleic acid to saturated stearic acid; the *cis*-9,*trans*-11 CLA formed as an intermediate of this process. Thus, it explains the presence of the *cis*-9,*trans*-11 CLA isomer in a number of food products from rumen origin, including beef, milk, and dairy products as well as foods from other rumen animals, and CLA intakes can vary greatly depending on dietary pattern (Chin et al. 1992). It has been estimated that the average total CLA intake in the United States from natural sources is ~200 mg/day for men and 93–151 mg/day for women and in the United Kingdom is 97.5 mg/day (Herbel et al. 1998, Mushtaq et al. 2010, Park et al. 1999b, Ritzenthaler et al. 2001).

Serum levels of CLA from subjects with low dairy or meat consumption were ~20 μM or 0.1% of total fatty acids (Mele et al. 2013, Zlatanos et al. 2008). It was also reported that serum CLA levels were higher in females than males, particularly in hormonal contraceptive users, and higher in Caucasians than Asians, which may be linked to Δ9-desaturase polymorphism, as the *trans*-11 vaccenic acid can be converted to the *cis*-9,*trans*-11 CLA isomer by this enzyme (Abdelmagid et al. 2013, Corl et al. 2003). The levels of the *cis*-9,*trans*-11 CLA isomer in adipose tissue, representing long-term exposure (>2 years), was 0.57% of fatty acids, without any presence of the *trans*-10,*cis*-12 isomer (Castro-Webb et al. 2012).

After supplementation of 0.8–3.2 g CLA per day for 2 months, serum levels of CLA ranged from ~50 to ~180 μM (Mele et al. 2013), which were comparable to serum CLA levels found in rats (23–120 μM) after supplementing CLA at 0.5 w/w% in diet for 4 weeks (Park et al. 1997). It was also reported that after withdrawing CLA supplementation for two months, serum CLA returned to control levels, consistent with results observed in animal studies (Mele et al. 2013, Park et al. 1999a).

UNDERSTANDING CONJUGATED LINOLEIC ACID ISOMERS

As mentioned in the previous section, the *cis*-9,*trans*-11 CLA isomer is the major isomer found in foods. However, there are a number of CLA isomers with double bonds at 7, 8, 9, 10, 11, 12, or 13 found in natural products (Dilzer & Park 2012, Eulitz et al. 1999). Among them, the most important isomer to address other than *cis*-9,*trans*-11 is the *trans*-10,*cis*-12 CLA isomer. This isomer is present in negligible amounts in foodstuffs. However, when CLA is prepared from linoleic acid (such as vege oils) using chemical processes, because of chemical stability a significant amount of this isomer is formed along with the other main isomer, *cis*-9,*trans*-11. Chemically prepared CLA contains approximately equal amounts of *cis*-9,*trans*-11 and *trans*-10,*cis*-12 isomers, typically 80–95% of total CLA, and other minor isomers, such as *trans*,*trans* isomers. This preparation is often referred to as CLA mixture or CLA 50:50, reflecting the presence of these two major CLA isomers. This is important, as naturally occurring CLA is present at very low concentrations, and it is necessary to prepare CLA by isomerization for further studies or applications. In fact, with the exceptions of a few CLA studies done in the late 1980s, most CLA investigations used CLA mixture. It was not until 1999 that scientists started to recognize the different roles of these two isomers (Bhattacharya et al. 2006, Park et al. 1999c). In the sections below, the role of these two major CLA isomers is addressed whenever results of the individual isomers are available.

There are currently limited reports of bioactivities for CLA isomers other than *cis*-9,*trans*-11 and *trans*-10,*cis*-12. Among them, *trans*,*trans* CLA isomers (either *trans*-9,*trans*-11 or a mix of *trans*,*trans*) are shown to have anticancer (Beppu et al. 2006, El Roz et al. 2013, Kim et al. 2008, Lai et al. 2005, Islam et al. 2010), anti-inflammation (Lee et al. 2009, Lee & Vanden Heuvel 2010), antiplatelet aggregation (Al-Madaney et al. 2003), and hypocholesterolemic effects, and to prevent fatty liver (Gilbert et al. 2011). Thus, we cannot exclude the potential activities of other minor CLA isomers.

APPLICATION OF CONJUGATED LINOLEIC ACID AS A FUNCTIONAL FOOD INGREDIENT

Current regulation of *trans* fat labeling by the US Food and Drug Administration defines *trans* fats as "all unsaturated fatty acids that contain one or more isolated double bonds (i.e., nonconjugated) in a *trans* configuration." Thus, the presence of CLA, which contains conjugated *trans* fatty acids, is exempt from the *trans* fat labeling. Moreover, CLA has been approved as generally recognized as safe (GRAS) for a mixture of approximately 60–90% of the *cis*-9,*trans*-11 and *trans*-10,*cis*-12 isomers in ~50:50. Consumption of up to 6 g CLA/day for 1 year or 3.4 g CLA/day for up to 2 years is currently considered to be safe based on previous clinical studies (Onakpoya et al. 2012, Park 2014, Schoeller et al. 2009, Whigham et al. 2007). The current GRAS claim is that "use of CLA-rich oil in certain specified foods within the general categories of soy milk, meal replacement beverages and bars, milk products and fruit juices, at a level of 1.5 g CLA per serving, is exempt." Thus, it is likely that CLA will be applied to a number of food products to improve the health perspectives discussed below. However, there are currently limited CLA-fortified foods available, reflecting some of the challenges of using CLA as a food ingredient (Moon et al. 2008).

HEALTH BENEFITS

Currently, almost 100 human studies have been published regarding CLA's effects (e.g., Dilzer & Park 2012, McCrorie et al. 2011, Park 2014). Human studies with CLA since 2012 are summarized in **Table 1** and are categorized by health benefits.

Table 1 Summary of publications on human studies with conjugated linoleic acid (CLA) since 2012

Reference	Study design and other subject information	CLA information			Results		Other results and comments
		Dose (g/day)	Duration (week)	Other notes	Obesity-related markers	Blood chemistry markers	
Obesity studies							
Carvalho et al. 2012	Randomized, hypocaloric diet, sedentary and metabolic syndrome	3	12	Micro-encapsulated	⇓ 3.32% BF mass[a]; no Δ weight, WC, or FFM	⇓ Insulin[a]; no Δ TC, LDL, HDL, or TG	No Δ HOMA-IR or BP
Chen et al. 2012	Randomized, double-blind	3.4	12	1.7 g CLA in 200 ml milk × 2	⇓ Weight (0.7kg)[a], BF (0.5kg), and BMI (0.32) without affecting WC or FFM	No Δ TC, LDL, HDL, TG, or Glu	Nonsignificant decrease on SBP w CLA (−3.6 mm Hg, p = 0.073) CLA reduces BMI better in subjects with >27 BMI No Δ AST or ALT
Macaluso et al. 2012	Cross-over, randomized, double-blind, 2-week washout, resistant exercise bout	6	3	NA	No Δ BF or FFM	NA	No Δ exercise outcome ⇑ Testosterone No Δ cortisol, estradiol, or SHBG
Bulut et al. 2013	Randomized, double-blind, 20 min aerobic exercise	3	4		No Δ BF, WC, BMI, or FFM	⇓ LDL[a,b], TG[a], and insulin[a,b]; no Δ TC, HDL, or Glu	⇓ Leptin[a,b] or HOMA-IR[a] No Δ LPL, or butyrylcholinesterase No additional effects of CLA beyond exercise
Lopez-Plaza et al. 2013	Randomized, double-blind	3	24	In 200 ml milk	⇓ Weight (0.89kg)[a], BF (1.12 kg), WC (0.8 cm), WHR (0.1), and BMI (0.63); no Δ FFM	No Δ TC, LDL, HDL, TG, or insulin; ⇑ Glu (2.66 mg/dl)[a]	No Δ HOMA-IR, leptin, adiponectin, CRP, PAI-1, ALT, or AST ⇑ Creatinine[a]
Shadman et al. 2013	Randomized, double-blind, overweight DM patients (>5 years) taking metformin	3	8	+ 100 U/d vitamin E	No Δ weight, BF, WC, BMI, or FFM	No Δ TG or insulin	No Δ HR, proinsulin, HOMA-IR, QUICKI, C-peptide, or β-cell response No Δ CRP, IL-6, IL-1β, TNF-α, adiponectin, fibrinogen, PAI-1, or leptin Nonsignificant ⇑ MDA

Jenkins et al. 2014a,b	Randomized, double-blind, 30 min aerobic exercise	5.63	6	NA	NA	⇓ TG[b]; no Δ Glu or TC	No Δ aerobic exercise performance by CLA No Δ exercise capacity, neuromuscular fatigue, or muscle endurance and power by CLA
Ormsbee et al. 2014	Randomized, double-blind	NA	8	Proprietary blend of CLA, green tea, caffeine, and BCAA	No Δ weight, BF, or FFM	No Δ TC, LDL, HDL, Glu, TG, or insulin	No Δ HR, HOMA-IR, leptin, adiponectin, or CRP ⇑ Hunger rating No Δ satiety, desire to eat, or mood
Falcone et al. 2015	Randomized, double-blind, moderately active women	NA	3	Mixture of protein gel, thermogenic, CLA, and multivitamin	⇓ Weight (2.96kg)[a,b], BF (1.99%)[a], and skinfolds (chest, waist, hip, subscapular, or tricep)[a,b]	NA	NA
Tajmanesh et al. 2015	Randomized, double-blind	3.2	12	NA	No Δ weight, BMI, or WC	NA	No Δ HR No Δ VO_{2max} or time to exhaustion
Tsao et al. 2015	Cross-over, randomized, 8-week washout, 60 min exercise	3.8	8	NA	NA	NA	Impaired glucose tolerance No Δ fat oxidation ⇓ NEFA[b], glycerol ⇑ Muscle glycogen[a,b]
Cardiovascular disease/insulin responses							
Bachmair et al. 2012	Randomized, double-blind	4	12	80:20	NA	NA	Significant alteration of proteins involved in cytoskeleton and platelet function (structure, receptor action, signaling, and focal adhesion)
Castro-Webb et al. 2012	Cross-sectional study	NA	NA	NA	NA	No difference in LDL or HDL; significant inverse correlation with c9,t11 CLA, and Glu and TG	232 DM and 1,512 Non-DM subjects in Costa Rica c9,t11 CLA in adipose tissue associated with lower DM risk

(*Continued*)

Table 1 (*Continued*)

Reference	Study design and other subject information	CLA information			Results		Other results and comments
		Dose (g/day)	Duration (week)	Other notes	Obesity-related markers	Blood chemistry markers	
Engberink et al. 2012	Cross-over, randomized	18.9	3	Food, *cis*9,*trans*11 only	NA		No Δ BP
Rubin et al. 2012	Cross-over, randomized, double-blind, 6-week washout, prediabetic	4.25	4	Mix or two separate isomers	⇓ WC by t10,c12; no Δ weight or BMI	No Δ TG, Glu, or insulin,	No Δ HOMA-IR, adiponectin ⇓ by t10,c12[b] PPARγ2 polymorphism influences responses to CLA
Pintus et al. 2013	Cross-over, randomized, single-blind, 3-week washout, hypercholesterol-emic subjects	~0.45–2.52	3	CLA from enriched sheep cheese, 45 or 90 g/d	NA	⇓ TC[a,b], LDL[a,b], and HDL[b]; no Δ TG	⇑ CLA and its metabolites in blood ⇓ Fatty acid hydroperoxides
Bachmair et al. 2015	Cross-over, randomized, double-blind, 4-week washout	4	2	80:20	No Δ weight or BMI	No Δ TC, LDL, HDL, or TG	No Δ BP or blood count No influence on markers of platelet functions
Inflammation/immune responses/oxidative stress							
Bassaganya-Riera et al. 2012a	Open, mild to moderate Crohn's	6	12	NA	NA	NA	⇓ Peripheral blood CD4+, and CD8+ T-cells[a], which produce IFNγ, TNFα, or IL-17 ⇓ Crohn's disease activity index ⇑ IBDQ, quality of life marker
Kim et al. 2012	Randomized, double-blind	2.4	8	NA	NA	NA	No difference in plasma TRAP, lipid peroxidation, lipid-soluble antioxidant vitamin contents, erythrocyte antioxidant enzyme activities, or leukocyte DNA damage

Eftekhari et al. 2013	Randomized, subjects w/coronary atherosclerosis	3	8	Comparison with 1.92 g ω-3	No Δ BMI	NA	⇓ CRP[a] and MDA by either CLA or ω-3 ⇓ IL-6 only by ω-3 ⇑ Glutathione peroxidase activity by either CLA or ω-3[a]
Penedo et al. 2013	Depletion-repletion study, 8-week depletion period	1.02	8	20 g/d enriched butter	No Δ BFM or BMI	No Δ Glu	⇑ IL-10[a] No Δ adiponectin, CRP, IL-4, hematocrit, or hemoglobin ⇓ NFκB[a], TNFα, IL-2, IL-8, MMT-9, or MMT-2
Aryaeian et al. 2014	Randomized, double-blind, rheumatoid arthritis patients	2.5	12	With vitamin E (400 mg)	NA	NA	No Δ serum vitamin E, MMP-3, or blood cell count by CLA or vitamin E alone CLA: ⇓ IL-4 and TNFα[a]; no Δ IL-1β or IL-2 CLA and vitamin E: ⇑ serum vitamin E[a]; ⇓ MMP-3, CCP-A, TNFα, IL-4, and WBC count[a]
Cancer							
Louw 2012	Cross-over, randomized, double-blind, 6-week washout, children, HPV-induced laryngeal papillomatosis	2.5	8-week and one-year follow-up	NA	NA	NA	⇓ Anatomical scores Relatively small sample size (n = 8)
Mohammad-zadeh et al. 2013	Randomized, double-blind, stage II–III rectal cancer patients	3	6	Treatment started 1 week prior to radio-therapy	NA	NA	No Δ ALT, AST, IL-1β, or MMP-2 ⇓ ALP[a,b], TNFα[a,b], CRP[b], and MMP-9[b]
McGowan et al. 2013	Open, stage I–III breast cancer patient	7.5	~4, >10 days prior to surgery	NA	NA	NA	⇓ S14 and Ki-67 in tumor tissue No Δ fatty acid synthase, LPL, or caspase-3 Safe up to 20 days

(*Continued*)

Table 1 (*Continued*)

Reference	Study design and other subject information	CLA information			Results		Other results and comments
		Dose (g/day)	Duration (week)	Other notes	Obesity-related markers	Blood chemistry markers	
Biological levels of CLA							
Ritzenthaler et al. 2012	Questionnaire	NA	NA	Diet, FFQ-2 weekday + 1 weekend day	NA	NA	Serum CLA levels: 0.46% in men, 0.54% in women in total lipid (fasting) CLA mostly in TG, correlates with intake in men but not in women Estimated mean chronic intake: 197 mg/d for men, 93 mg/d for women or 151 mg *cis*9,*trans*11/d for men, 72 mg *cis*9,*trans*11/d for women
Abdelmagid et al. 2013	Cross-sectional study, serum levels	NA	NA	NA	NA	NA	Serum CLA levels: 13–22 μM of *cis*9,*trans*11, 4–4.3 μM of *trans*10,*cis*12 CLA levels higher in females, higher in hormonal contraceptive users, higher in Caucasian than Asian Δ9-Desaturase polymorphism linked with reduced *cis*9,*trans*11 in Caucasian males
Mele et al. 2013	Randomized	0.8, 1.6, 3.2	8	80:20	NA	No Δ TC, LDL, or HDL	Serum CLA levels: 0.8 g CLA/d, 50 μM, 3.2 g CLA/d, ∼280 μM Returns to control level after 2-month washout period Metabolites of CLA (conjugated 16:2, conjugated 18:3, conjugated 20:3) increased with CLA supplementation

[a]Significantly different within group.
[b]Significantly different between groups.
Abbreviations: Δ, change; ⇓, decrease; ⇑, increase; ALT, alanine transaminase; AST, aspartate transaminase; BCAA, branched chain amino acid; BFM, body-fat mass; BMI, body mass index; BP, blood pressure; CCP-A, citrullinated antibodies; CD, cluster of differentiation; CLA, conjugated linoleic acid; CRP, C-reactive protein; DM, diabetes mellitus; FFM, fat-free mass; FFQ, food frequency questionnaires; Glu, glucose; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HPV, human papilloma virus; HR, heart rate; IFNγ, interferon-γ; IBDQ, inflammatory bowel disease questionnaire; IL, interleukin; LDL, low-density lipoprotein cholesterol; LPL, lipoprotein lipase; MDA, malondialdehyde; MMT, matrix metalloproteinase; NA, not available; NEFA, nonesterified fatty acid; NFκB, nuclear factor kappa B; PAI-1, plasminogen activator inhibitor-1; PPARγ, peroxisome proliferator–activated receptor-γ; SHBG, sex hormone–binding globulin; SPB, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TNFα, tumor necrosis factor-α; TRAP, total radical-trapping antioxidant potential; VO_{2max}, maximal oxygen consumption; WBC, white blood cell; WC, waist circumference; WHR, waist-hip ratio.

Antiobesity Effects of Conjugated Linoleic Acid

Since the antiobesity effect of CLA was first reported by Dr. Pariza's group in 1997 (Park et al. 1997), it has been the main focus of CLA interest. Although overall results from human studies on the antiobesity effects of CLA are somewhat weak compared with those from animal studies, a number of clinical trials reported positive correlations between CLA supplementation as well as an improvement in body mass index (BMI), body weight, body-fat mass (BFM), abdominal adiposity, and lean body mass (LBM) (Bhattacharya et al. 2006, Dilzer & Park 2012, McCrorie et al. 2011, Onakpoya et al. 2012, Park 2014, Schoeller et al. 2009, Whigham et al. 2007). As such, three meta-analyses of previous human studies concluded that CLA supplementation induced modest, but significant, loss in body weight and BFM when CLA was supplemented at 3.2–3.4 g/d for at least 6 months (Onakpoya et al. 2012, Schoeller et al. 2009, Whigham et al. 2007). Because of this, there have been more efforts to combine CLA with other tools known to assist in obesity control, such as specific treatments or compounds, distinct delivery systems, or physical activity, to improve its efficacy. Carvalho et al. (2012) reported that using microencapsulated CLA (3 g/d) resulted in a significant reduction in BFM in women with metabolic syndrome after only 30 days.

There are a number of studies reporting CLA's mechanisms on antiobesity effects: reduced energy intake, increased energy expenditure, modulated lipid/adipocyte metabolism, and/or altered skeletal muscle metabolism (Bhattacharya et al. 2006, Park & Pariza 2007). There are inconsistent reports of CLA's effects on food intake, particularly in mice, which may be independent from appetite-regulating neuropeptides in the hypothalamus (Park et al. 1997, Shelton et al. 2012). However, it has been suggested that CLA's effect on food intake was not responsible for its role in body-fat reduction in mice (Park et al. 2007). There are several reports of CLA and reduced caloric intake in humans; however, other studies did not find any effects of CLA on calorie intake (Dilzer & Park 2012, Park 2014). Similarly, CLA increased total energy expenditure in animal models but not in humans (Dilzer & Park 2012, Park 2014, Park & Park 2010).

Currently, there are a significant number of studies reporting CLA's effects on both adipocyte and skeletal muscle metabolisms, which can help explain its role in body composition changes (Bhattacharya et al. 2006, Dilzer & Park 2012, Park & Pariza 2007). These include the effects of CLA on the reduction of lipid storage, synthesis, and adipogenesis in adipocytes, and on enhanced fat utilization in muscle via fatty acid β-oxidation (Park & Pariza 2007). The isomer-specific studies revealed that the *trans*-10,*cis*-12 isomer is responsible for CLA's role in the modulation of body composition, but the *cis*-9,*trans*-11 isomer has no effect (Park et al. 1999c). It is also interesting that dietary *trans*-10,*cis*-12 CLA increases browning of adipocytes in mice, which further helps explain its role in decreased adiposity (Shen et al. 2013, 2015). To establish the effective CLA usage as an antiobesity agent for humans, further studies are needed to determine the conditions and strategies to improve CLA's efficacy on body-fat regulation.

Effects of Conjugated Linoleic Acid on Muscle Metabolism

Skeletal muscle accounts for nearly 40% of total body mass and plays a significant role in overall energy metabolism (Matsakas & Patel 2009). Previous observations imply that CLA supplementation may target skeletal muscle for CLA's effects, including increased lean body mass (representing skeletal muscle mass), energy expenditure, voluntary activity, endurance capacity, fatty acid β-oxidation, and, more recently, mitochondrial biogenesis compared with control animals (Bhattacharya et al. 2005, 2006; Kim et al. 2012; Kim & Park 2015; Vaughan et al. 2012). These effects of CLA have been suggested to be associated with its role in AMP-activated protein kinase (AMPK), which is a major regulator for energy and muscle metabolisms. Activation of AMPK by CLA subsequently activates PPARγ coactivator-1α (PGC-1α) and peroxisome proliferator

activated receptor-δ (PPARδ), resulting in alteration of lipid metabolism, mitochondrial biogenesis, and/or muscle fiber–type transformation from glycolytic fast-twitch type II (fewer mitochondria) to oxidative slow-twitch type I fibers (more mitochondria) (Huang et al. 2014, Kim & Park 2015, Men et al. 2013, Mohankumar et al. 2013, Qin et al. 2009). This effect of CLA on skeletal muscle may have significant implications for how CLA controls body fat while improving lean body mass.

Currently, clinical trials reporting the effects of CLA on lean body mass or exercise outcome were not consistent, including recent reports in **Table 1** (Bulut et al. 2013; Dilzer & Park 2012; Jenkins et al. 2014a,b; Macaluso et al. 2012; McCrorie et al. 2011; Park 2014; Tajmanesh et al. 2015; Tsao et al. 2015). However, these studies, with the exception of Tarnopolsky et al. (2007), used a relatively short-term supplementation (12 weeks or shorter). Based on the outcomes of recent animal studies on muscle metabolism, more human studies on long-term (longer than 6 months) supplementation are needed to confirm CLA's effect on muscle metabolism. These studies may also strengthen the understanding of CLA's role in body-fat regulation.

Prevention of Age-Associated Health Issues

Prevention of cardiovascular diseases by conjugated linoleic acid. Since the first reports of CLA's reduction of atherosclerotic lesions in rabbits, a number of animal studies followed, as atherosclerosis is the leading symptom associated with development of cardiovascular diseases in the United States (Bhattacharya et al. 2006, Dilzer & Park 2012, Lee et al. 1994, McCrorie et al. 2011, Park 2014). The majority of CLA clinical studies found that CLA did not influence blood lipid markers for cardiovascular diseases, such as total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and/or triacylglyceride (TG). This is consistently shown in recent publications as well (see **Table 1**), with most reporting no changes of these markers but a few reported decreases in total cholesterol, LDL, and/or TG after CLA treatment (Bulut et al. 2013, Jenkins et al. 2014b, Pintus et al. 2013).

It is important to point out that previous studies reported an association between CLA and increased C-reactive protein (CRP), although recent publications (see **Table 1**) reported no correlation between CRP and CLA (Dilzer & Park 2012, Lopez-Plaza et al. 2013, McCrorie et al. 2011, Ormsbee et al. 2014, Park 2014, Shadman et al. 2013). Increased CRP is known to be associated with adverse health consequences, and this needs to be carefully addressed. However, it has been suggested that CLA increased CRP without altering other markers, suggesting that CLA supplementation does not increase the risk for cardiovascular disease (Park 2014). Moreover, Smit et al. (2010) reported an inverse association between adipose tissue *cis*-9,*trans*-11 CLA and risk of myocardial infarction among Costa Rican subjects.

A recent meta-analysis concluded that CLA had no positive effects on blood pressure in humans (Yang et al. 2015). However, two reports by Herrera et al. (2005, 2006) showed benefits of CLA supplementation on pregnancy-induced hypertension. In addition, Zhao et al. (2009) reported cosupplementation of CLA and an antihypertensive drug (ramipril) effectively reduced blood pressure via decreased serum angiotensinogen in hypertensive patients. Among recent publications, Chen et al. (2012) reported a nonsignificant decrease of systolic blood pressure with CLA supplementation ($p = 0.073$), whereas other studies reported no effects of CLA on blood pressure (Bachmair et al. 2012, Carvalho et al. 2012, Engberink et al. 2012, Shadman et al. 2013). Based on these reports, the roles of CLA in the risk of cardiovascular diseases, including its role in blood pressure regulation, is not conclusive for humans.

Menopause and conjugated linoleic acid. Estrogen, the female sex hormone, plays numerous physiological roles in the reproductive, cardiovascular, skeletal, and central nervous systems. At

menopause, the loss of endogenous estrogen production causes a number of health issues, including hot flashes, sleep disturbances, osteoporosis, and metabolic disorders (Al-Safi & Santoro 2014). Although currently relatively limited, preclinical and clinical evidence suggest protective effects of CLA against postmenopausal bone loss and metabolic dysfunctions as well as inhibition of breast and endometrial cancer cell growth (Kim et al. 2015).

Osteoporosis is one of the major health concerns associated with menopause. CLA has been shown to improve bone formation and prevent bone resorption in both ovariectomy and age-associated bone loss in animal models (Halade et al. 2011; Kelly & Cashman 2004; Park et al. 2013; Rahman et al. 2007, 2011, 2014). In addition, the positive interaction between CLA and calcium supplementation in the regulation of bone metabolism and the preferable changes toward more osteoblastogenesis and less osteoclastogenesis by CLA were reported (Kim et al. 2013; Rahman et al. 2007, 2011). There is currently one human study regarding CLA and bone health, particularly for naturally occurring CLA, with postmenopausal women, where the beneficial effect of dietary CLA on bone mineral density was reported (Brownbill et al. 2005).

Along with its role on postmenopausal bone loss, CLA has also been shown to alleviate menopause-associated obesity and metabolic disorders (Kanaya & Chen 2010, Norris et al. 2009, Raff et al. 2009, Tholstrup et al. 2008). Animal studies demonstrated that the body fat lowering effect of CLA was observed in ovariectomized mice similar in manner to its effects in a sham model (Kanaya & Chen 2010, Park et al. 2013). This suggests that CLA has an antiobesity effect in mice independent of estrogen levels. For healthy or obese postmenopausal women, CLA supplementation had a significant effect on lowering BFM (Norris et al. 2009, Raff et al. 2009).

Because hormone replacement therapy used for menopause is often associated with increased breast or endometrial cancer risk (Folkerd & Dowsett 2013, Pickar et al. 2003), CLA's effect on the regulation of ER signaling pathways has been studied for CLA's anticancer effects, particularly breast cancer (Kim et al. 2015). CLA increased protein phosphatase 2A (PP2A) activity to dephosphorylate ERα, which subsequently reduced binding affinity to estrogen response elements and suppressed the transcriptional activation of ERα target genes, resulting in inhibition of cell growth and increased apoptosis in ER-positive breast cancer cells (Liu & Sidell 2005, Miglietta et al. 2006, Tanmahasamut et al. 2004). Others reported that the *trans*-10,*cis*-12 CLA inhibited estrogen-induced cell proliferation in ER-positive MCF-7 human breast cancer cells, but *cis*-9,*trans*-11 CLA had no inhibitory effect (Chujo et al. 2003). In addition, the combination treatment of *trans*-10,*cis*-12 CLA and tamoxifen (selective estrogen receptor modulator) showed synergistic effects on the suppression of estrogen-stimulated carcinogenic responses in MCF-7 cells (Wang et al. 2008). These findings suggest that CLA may have potential to act as an estrogen antagonist in estrogen-sensitive target cells, resulting in prevention of estrogen-dependent types of breast cancer. Despite evidence of CLA's effects in human cancer cells, the majority of human studies reported no CLA effects on breast cancer incidence in postmenopausal women (Chajes et al. 2003, McCann et al. 2004, Rissanen et al. 2003), except one reporting that CLA-rich diets protect against breast cancer in postmenopausal women (Aro et al. 2000). Based on this, CLA has potential to provide beneficial effects on postmenopausal bone loss and metabolic dysfunctions while potentially protecting against breast cancer associated with estrogen. To determine the efficacy and safety of CLA supplementation in postmenopausal women, however, the influences of CLA on breast cancer risk in postmenopausal women receiving estrogen treatment must be evaluated.

Anticancer effects of conjugated linoleic acid. In addition to its effects on breast cancer in postmenopausal women, there has been significant interest in CLA studies on cancer prevention (Bhattacharya et al. 2006, Lee et al. 2005, McCrorie et al. 2011, Moon 2014). However, there are only a limited number of human studies involving CLA and cancer (Bhattacharya et al. 2006, Dilzer

& Park 2012, McCrorie et al. 2011). Most of these studies investigated the correlation between dietary intake of CLA or tissue CLA levels and breast cancer incidences in which inconsistent trends were found. McGowan et al. (2013) is the only report of a CLA clinical trial for breast cancer. Breast cancer patients (stage I–III) were given CLA supplementation (7.5g/day) prior to surgery, and the effects of CLA on fatty acid metabolism and S14, a marker of breast cancer, were observed. S14 is associated with lipid metabolism and correlated with the recurrence of cancer in and survival of breast cancer patients. They found that CLA supplementation at least 10 days prior to surgery was associated with reduced S14 levels in tumor tissue in patients with higher cancer scores (II), but not in patients with lower cancer scores (I), without any indication that CLA influenced fatty acid synthase or lipoprotein lipase expression. This study also reported that Ki-67 (tumor proliferation marker) was decreased after CLA supplementation without changing caspase 3 (an apoptosis marker) in these patients. Based on these observations, they concluded that CLA may be used in conjunction with current options for breast cancer treatment.

Larsson et al. (2005) was the first to report a negative correlation between consumption of high fat dairy and CLA and incidences of colorectal cancer. Mohammadzadeh et al. (2013) reported that supplementation of CLA, 3g/day for 6 weeks, to rectal cancer patients (Stage II–III) during chemoradiotherapy significantly reduced matrix metalloproteinase (MMP)-2 and -9, suggesting that CLA potentially reduced angiogenesis and tumor invasion. This finding was further supported by Penedo et al.'s (2013) report. Also, CLA supplementation was associated with reduced serum tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and/or C-reactive protein, implying that CLA may prevent inflammatory responses associated with radiotherapy (Mohammadzadeh et al. 2013, Penedo et al. 2013).

There is a report of the potential preventive effects of CLA on children with laryngeal papillomatosis in South Africa, which is particularly associated with human papillomavirus (HPV) and can cause airway obstruction in young children (Louw 2012). Although this study was done with a very limited number of subjects, the results showed that CLA treatment resulted in significantly lower anatomical scores of HPV-induced laryngeal papillomatosis. These human studies suggest the potential application of CLA in cancer patients, either alone or as a part of current anticancer treatments.

Sarcopenia/sarcopenic obesity and conjugated linoleic acid. Sarcopenia is the condition describing the age-dependent gradual loss of skeletal muscle mass resulting in decreased muscle strength, often associated with the loss of independent living ability for the elderly as well as increased risk of falls and fractures (Narici & Maffulli 2010). The prevalence of sarcopenia is estimated at approximately 15% for adults under 70 years and increases to greater than 50% in those over 80 years (Houston et al. 2009). More significantly, age-related obesity in the elderly is often associated with sarcopenia, which is defined as sarcopenic obesity. In sarcopenic obesity, the risks of disability, morbidity, and mortality are greater than those of sarcopenia and obesity combined (Houston et al. 2009, Narici & Maffulli 2010).

Based on previous reports that CLA has been shown to prevent age-associated obesity and muscle loss in mice models, CLA has the potential to prevent sarcopenia and sarcopenic obesity (Halade et al. 2009, Park & Park 2010, Rahman et al. 2009). In human studies, Tarnopolsky et al. (2007) reported that cosupplementation of CLA and creatine monohydrate for 6 months in older subjects (65–85 years) reduced BFM and increased lean mass. Two studies with postmenopausal women reported reduced BFM but inconsistent effects on fat-free mass (Norris et al. 2009, Raff et al. 2009). Similarly, Sneddon et al. (2008) compared effects of CLA (when cosupplemented with ω-3 fatty acids) in young and old subjects. They found no significant effects of CLA and ω-3 fatty acids in older obese subjects, but found reduced BFM and increased lean mass in young

obese subjects. Although it may be limited, along with other effects of CLA on lipid and muscle metabolisms (in the earlier section), application of CLA for preventing sarcopenia and sarcopenic obesity may be significant, as there are currently only very limited treatment options for these conditions (Houston et al. 2009, Narici & Maffulli 2010).

Other Functions of Conjugated Linoleic Acid

Improved immune and inflammatory responses. CLA has been shown to alleviate adverse effects of immune stimulation, reducing inflammatory responses as well as hypersensitivity in animal models (Bhattacharya et al. 2006). However, there are limited reports of CLA with regard to improved immune responses in humans, which include suppressing allergic responses, enhancing antibody production following vaccination, reducing symptoms of atopic dermatitis, and reducing symptoms of rhinovirus infection (Asp et al. 2011, Dilzer & Park 2012, McCrorie et al. 2011, Smit et al. 2011, Sofi et al. 2010). Recent clinical studies have shown that CLA decreases major proinflammatory markers, such as TNF-α or nuclear factor kappa B (NFκB), even in rheumatoid arthritis patients (Aryaeian et al. 2014, Penedo et al. 2013). Cosupplementation of CLA and vitamin E in patients with rheumatoid arthritis significantly decreased markers for arthritis, such as citrullinated antibodies (CCP-A), matrix metalloproteinase 3 (MMP-3), and white blood cell counts (Aryaeian et al. 2014). This suggests that CLA supplementation, along with current efforts, has potential to be used to manage symptoms of rheumatoid arthritis.

There are reports on effects of CLA and inflammatory bowel disease (Bassaganya-Riera et al. 2004, Bassaganya-Riera & Hontecillas 2006). Approximately 1.4 million Americans have inflammatory bowel disease, primarily Crohn's disease and ulcerative colitis (Abraham & Cho 2009). Because current treatments of inflammatory bowel disease are rather limited with potentially severe adverse effects, there is great need to identify the tools or treatment options for maintaining proper inflammatory responses to prevent or reduce symptoms of inflammatory bowel disease (Abraham & Cho 2009). Along with previous observations that CLA decreases adverse immune and inflammatory responses, this suggests that CLA may be helpful in reducing symptoms of inflammatory bowel disease.

There is a clinical trial that studied CLA's effect on Crohn's disease (Bassaganya-Riera et al. 2012a), where supplementation of 6 g CLA/day for 12 weeks decreased Crohn's disease activity index as well as improved inflammatory bowel disease questionnaire responses (representing improved quality of life). This was associated with decreased inflammatory cytokines such as interferon-γ, TNF-α, and IL-17. Penedo et al. (2013) consistently reported that subjects who consumed 20 grams a day of naturally enriched butter for 8 weeks for the *cis*-9,*trans*-11 CLA showed decreased serum levels of TNF-α, NFκB, IL-2, and IL-8. These results suggest that CLA, including naturally occurring isomers, may contribute to reduced inflammatory responses and potentially be helpful in alleviating symptoms associated with inflammatory bowel disease. Alternatively, the intestinal gut microbiota is known to play a significant role in the development of inflammatory bowel disease as well (Khor et al. 2011). Because it has been reported that CLA influences microbiota composition, it is possible that CLA may modulate disease progression via a microbiota-mediated mechanism (Bassaganya-Riera et al. 2012b, Marques et al. 2015). With the known link between inflammatory bowel disease and an increased risk of developing certain types of colorectal cancer (Evans et al. 2010), the application of CLA to control inflammatory bowel disease is of significant interest, possibly leading to reduced risk of developing colorectal cancer.

Steroidogenetic and other effects of conjugated linoleic acid. There are two studies that investigated CLA supplementation and its steroidogenetic effects (Barone et al. 2013, Macaluso

et al. 2012). They reported that CLA treatment increased testosterone secretion in Leydig cells via upregulation of CYP17A1 (Barone et al. 2013, Macaluso et al. 2012). This may be linked to CLA's effect on muscle metabolism or exercise outcome. In addition, Hwang et al. (2012) reported an interesting role of CLA in the prevention of proinflammatory responses associated with *Helicobacter pylori* in gastric epithelial cells. This potentially links to reduced development of stomach cancer in those with *H. pylori* infection.

POTENTIAL HEALTH CONCERNS OF CONJUGATED LINOLEIC ACID

Currently, four aspects of CLA supplementation are of concern; glucose homeostasis, oxidative stress, fatty liver (hepatic steatosis), and milk-fat depression. GRAS exemption of CLA has been based on all available data including these of potential adverse effects. Below each of these are summarized briefly.

Glucose Homeostasis

The effects of CLA on glucose homeostasis have not been consistent in either animal or human studies (Bhattacharya et al. 2006, Dilzer & Park 2012, McCrorie et al. 2011, Park 2014, Park & Pariza 2007). The majority of studies reported no association of glucose or insulin levels with CLA supplementation (Dilzer & Park 2012, McCrorie et al. 2011, Park 2014, Riserus et al. 2002a). Similarly, some recent studies have shown that CLA has no effect on glucose homeostasis (Carvalho et al. 2012; Chen et al. 2012; Jenkins et al. 2014a,b; Lopez-Plaza et al. 2013; Ormsbee et al. 2014; Shadman et al. 2013); however, other studies report reduced homeostatic model assessment (HOMA) or impaired glucose tolerance with CLA supplementation along with exercise (Bulut et al. 2013, Tsao et al. 2015).

Previously, it was reported that the potential adverse effects of CLA on glucose homeostasis is particularly linked to the *trans*-10,*cis*-12 CLA isomer (Riserus et al. 2002a,b). The *cis*-9,*trans*-11 isomer has consistently shown no association with glucose homeostasis; however, this isomer may antagonize the *trans*-10,*cis*-12 isomer when used as a mixture (Riserus et al. 2002a; Riserus et al. 2004a,b). Moreover, Castro-Webb et al. (2012) reported an inverse correlation between the levels of the *cis*-9,*trans*-11 CLA isomer in adipose tissue and the risk of diabetes. In addition, it has been suggested that the effects of CLA on glucose homeostasis are transient because of metabolic changes associated with CLA's effect on lipid metabolism. In addition, the safety of CLA usage, particularly for the two-isomer mixture, for glucose homeostasis has been proven in relatively long-term studies in humans (>6 months) (Gaullier et al. 2004, 2005; Park 2014; Whigham et al. 2004).

Oxidative Stress

There are consistent reports that both isomers of CLA are associated with increased isoprostanes, markers of oxidative stress, such as 8-iso-prostaglandin $F_{2\alpha}$ (nonenzymatic) and/or 15-ketodihydro-$PGF_{2\alpha}$ (enzymatic) from serum or urine samples (Dilzer & Park 2012, Park 2014). However, CLA supplementation did not alter other oxidative stress markers, such as levels of oxidized LDL, serum lipid peroxidation [as malondialdehyde (MDA)], or serum antioxidant concentrations (Aryaeian et al. 2014, Kim et al. 2012, Pfeuffer et al. 2011, Shadman et al. 2013). Eftekhari et al. (2013) reported decreased MDA levels and increased glutathione peroxidase activity after CLA supplementation that were similar to those of ω-3 fatty acid supplementation. Based on observations that CLA is metabolized to structural analogs of isoprostanes and that there

was no significant increase in other oxidative markers, it has been suggested that CLA might not represent an actual risk of oxidative stress (Banni et al. 2004, Sebedio et al. 2001).

Hepatic Steatosis

Some studies have shown a connection between CLA and enlarged liver as nonalcoholic fatty liver (hepatic steatosis) in mice (Adkins et al. 2013, Go et al. 2013, Kostogrys et al. 2012, Larsen et al. 2003, Li et al. 2012; Vyas et al. 2012). This is particularly associated with the *trans*-10,*cis*-12 isomer (Go et al. 2013, Kostogrys et al. 2012, Vyas et al. 2012). This association of CLA and hepatic steatosis was suggested to be linked to increased fat mobilization from adipose tissue accompanied with increased hepatic lipogenesis, increased long-chain fatty acid update, and increased TG synthesis (Go et al. 2013, Li et al. 2012, Vyas et al. 2012). O'Hagan & Menzel (2003) reported that fatty liver associated with CLA may be an adaptive response to CLA, which is reversible. Mollica et al. (2014) reported that CLA supplementation reduced signs of high-fat diet–induced hepatic steatosis in rats, more effectively with the *cis*-9,*trans*-11 isomer but even with the *trans*-10,*cis*-12 isomer. Also, Fedor et al. (2012) reported cosupplementation of docosahexaenoic acid prevented CLA-induced hepatic steatosis.

Currently, there are three reports of human cases of CLA-induced hepatitis (Bilal et al. 2015, Nortadas & Barata 2012, Ramos et al. 2009). However, there are multiple clinical trials, including one- and two-year studies, reporting markers of liver functions after CLA supplementation with no changes or minimal increases within the normal ranges (Chen et al. 2012; Dilzer & Park 2012; Gaullier et al. 2004, 2005; Lopez-Plaza et al. 2013; Mohammadzadeh et al. 2013; Onakpoya et al. 2012; Wanders et al. 2010). Malpuech-Brugere et al. (2004) reported no significant changes in liver structure, morphology, or signs of lipodystrophy after 18 weeks of CLA supplementation. Wanders et al. (2010) also reported a high dose of CLA (14.6 g *cis*-9,*trans*-11 and 4.7 g *trans*-10,*cis*-12 CLA per day) for 3 weeks had no adverse effects on liver function in healthy subjects. These discrepancies may be due to different doses used in rodents and humans, or mice in particular are much more sensitive to CLA's effect.

Milk-Fat Depression

As shown in body-fat reduction, CLA reduces quantity of total milk fat, described as milk-fat depression, observed not only in cows but also in goats and mice (Baldin et al. 2013, Bauman & Griinari 2003, Bernard et al. 2008, Harvatine et al. 2014). This prompted questions about the use of CLA in humans with regard to the health of infants. However, it has been suggested that there are major differences in milk-fat origin between ruminants and humans. De novo fatty acid synthesis plays a major role on ruminant milk fat, while dietary fat plays a major role in human milk-fat, which makes milk-fat contents from ruminants more sensitive to CLA (Bauman & Griinari 2003, Bernard et al. 2008, Hachey et al. 1989).

Currently, there are four papers on CLA and milk-fat content in humans (Hasin et al. 2007, Masters et al. 2002, Mosley et al. 2007, Ritzenthaler et al. 2005). Among them, Masters et al. (2002) reported that 1.5 g CLA/day for 5 days significantly reduced milk fat compared with a placebo, although milk-fat levels were still within the normal range. Others reported no differences in milk-fat content after CLA supplementation (2–4 g/day or 750 mg CLA isomers/day) for 5 days (Hasin et al. 2007, Mosley et al. 2007). A study by Ritzenthaler et al. (2005) reported no effects of CLA, although they were testing the naturally occurring CLA, which is not responsible for reducing fat levels (Harvatine et al. 2014, Park et al. 1999c). With these limited studies and with the limitations of long-term human trials because of ethical issues, it may be difficult to conclude that CLA has significant impact on human milk-fat content.

CONCLUSIONS

Based on current knowledge of CLA's activities, CLA is used for a number of health issues. More recent findings suggest that the combining of CLA with other known treatments or with prevention tools may further expand its applications. CLA has great potential to improve the health issues of the elderly, particularly with regard to symptoms of menopause, bone health, sarcopenia, and sarcopenic obesity, but this potential is still underexplored. With application to food products, CLA consumption is expected to increase; therefore, not only known potential adverse effects but also unknown consequences should be closely monitored to ensure proper application of CLA.

DISCLOSURE STATEMENT

Dr. Yeonhwa Park is one of the inventors of CLA-use patents that are assigned to the Wisconsin Alumni Research Foundation. Jun Ho Kim, Yoo Kim, and Young Jun Kim are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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