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What is the Safety and Efficacy of Conjugated Linoleic Acid Used for Weight Loss supplements?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABTRACT

OBJECTIVE: The objective of this systematic review is to determine the safety and efficacy of conjugated linoleic acid for weight loss in obese individuals.

STUDY DESIGN: Review of three English language primary studies published in 2004 and 2006.

DATA SOURCES: Randomized, double-blind, placebo-controlled trials comparing conjugated linoleic acid to placebo were found using OVID MEDLINE and Cochrane Databases.

OUTCOMES MEASURED: Conjugated linoleic acid efficiency and adverse effects. In each study, change in body weight, BMI, vital signs, and complete blood work was conducted at the beginning, during set intervals, and at the end of the study. Adverse effects were measured by a questionnaire used in each study at different intervals and at the end of the study. Blood work was also examined for any adverse change in glucose, insulin, AST, and ALT levels.

RESULTS: Two studies found that conjugated linoleic acid is effective for weight loss. All three trials found that there were no significant adverse effects or change in glucose, insulin, AST, and ALT with long-term conjugated linoleic acid usage.

CONCLUSIONS: Conjugated linoleic acid has the potential to be an effective weight loss supplement in obese individuals, but further studies are needed to determine its true efficiency. Studies are needed that contain specific age ranges, equal gender distribution, and a variety in the amount of conjugated linoleic acid studied. The results demonstrate that conjugated linoleic acid is a safe drug to use, with minimal adverse effects.

KEY WORDS: conjugated linoleic acid, CLA, efficiency, safety, adverse effects, and obesity

INTRODUCTION

Obesity is the leading cause of preventable death worldwide. Obesity affects over 75.2 million people, or about 65% of the population, in the United States. Obesity can lead to a variety of diseases, including cardiovascular disease, diabetes mellitus type 2, obstructive sleep apnea, certain cancers, and osteoarthritis. This condition has also been shown to reduce life expectancy on average of up to 8 to 10 years. From 1987 to 2001, medical costs associated with obesity accounted for 27% of the increases in medical costs in the U.S. In 2006, it was found that medical costs for obesity were estimated to be $147 billion dollars. Obese persons have estimated medical costs that are $1,429 higher than non-obese persons. In 2009, it was found that at least 30% of adults were obese in nine states, compared to zero states in 2000. In 2009, over 65 million healthcare visits were obesity related[1].

Obesity is characterized by excess body fat that accumulates and leads to adverse health conditions. On the BMI scale, obesity is classified as over 30 kg/m^2. Obesity has been considered a direct result of a sedentary lifestyle with ingestion of excess calories. However, several studies have shown a genetic link with the development of obesity, with as much as 40-70% of obesity explained by genetic influences. Five genes affecting appetite have been discovered in mice, including the gene leptin, which codes for a protein that is expressed by adipose tissue. When an individual has a deficiency or resistance in leptin, it is thought that the individual overfeeds, eventually leading to obesity. However, current literature suggests obesity develops multifactorially, from a combination of genes, the environment, and behavior[2].

Most successful weight loss comes from a combination of low caloric diets, behavior modification, exercise, and social support. Due to high relapse rates, much emphasis must be placed on the maintenance of weight loss over time. Several medications have been approved by

the FDA, including short-term anticholaminergic medications such as phentermine, diethylpropion, and mazindol. Two long-term medications include sibutramine, which blocks the uptake of serotonin and norepinephrine in the central nervous system, and orlistat, which reduces fat absorption. Over the counter medications include bitter orange extract, chitosan, chromium, conjugated linoleic acid (CLA), among many others. Bariatric surgery may also be indicated in the morbidly obese, and can result in over 50% of body weight loss after one year[2].

While the above prescription medications are effective, only 20% of patients using these prescription medications will lose 20 lb and maintain the loss for only 2 years, even with diet and exercise. Average weight loss using diet and exercise alone is about 7% of initial baseline weight, and many of these patients even after the 7% loss will still continue to have a BMI in the obese category[2]. Currently, there are no long-term studies to support that prescription medication can maintain long-term weight loss. Sibutramine, which is no longer available, contained many side effects, including dry mouth, anorexia, constipation, insomnia, and dizziness. Orlistat has been linked to the proliferation of aberrant crypt foci, which are precursors to colon cancer. Up to 40% of patients who receive bariatric surgery experience side-effects, including post-operative wound infections, gastric bleeding, and death[3]. However, an over-the-counter supplement, conjugated linoleic acid, may provide satisfactory weight loss that causes less adverse effects than prescription medications or surgery. CLA is the first ingredient listed in many popular over-the-counter weight loss supplements, and is also sold in a pill form.

OBJECTIVE

The objective of this systematic review is to determine “the safety and efficacy of conjugated linoleic acid used for weight loss in obese individuals”.

METHODS

The criteria for selection of the studies included obese patients who are otherwise healthy between the ages of 18-65 years. Inclusion criteria for each of the studies utilized BMI, however, each criteria was slightly different. Gaullier et al. accepted subjects with a BMI range of 28-32 kg/m^2, Watras et al. accepted a BMI range of 25-30 kg/m^2, and Whigham et al. accepted a BMI of 27 – 35 kg/m^2. Each study had exclusion criteria of any subjects on drug therapy were not able to participate. The Gaullier et al. and Whigham et al. studies also excluded pregnant subjects and patients with serious medical conditions.

The intervention used was the administration of CLA for weight loss. In each study, results are compared between the groups receiving CLA 3.4g/day (Gaullier et al.)[4], CLA 4g/day (Watras et al.)[5], or 6g/day (Whigham et al.)[6]against a placebo. According to the patients in all three studies, CLA is a safe method for weight loss reduction. CLA was an effective weight loss supplement in both the Gaullier et al. and Watras et al. studies, however, in the Whigham et al. study, patients did not have any significant weight change. The types of studies included were randomized control trials, double-blind, and placebo-controlled.

The three randomized control trials in this review were all double-blind clinical trials with the intention to treat and with subjects being either overweight or obese based on clinical criteria. The Gaullier et al. study had the greatest number of participants with 118, and a withdrawal of 25. Whigham et al. started with 64 participants, and had 8 withdrawals. The Watras et al. study had 48 patients and had 8 withdrawals. In the Gaullier study, participants were given 3-4 g/CLA a day, while Whigham et al. administered 3.2g/CLA a day, and Watras et al. administered each participant 6g/CLA a day.

Key words in the literature searches were conjugated linoleic acid, CLA, body composition, overweight, safety, efficacy, adverse effects, and obesity. All articles searched were in peer-reviewed journals and all articles were published in English. Literature searches were conducted using the OVID MEDLINE and Cochrane databases. Articles were selected based on relevance and that the outcomes of the studies mattered to patients (POEMS). Articles that were published before October 2002 were excluded due to a Meta-Analysis written at that time. Studies included were conducted in a randomized, controlled fashion in a prospective, intention-to-treat basis, dated after Oct. 2002. Statistics used to report the data included *p* values, Fisher's exact test, a X^2 test, a *t*-test, and numbers needed to treat (NNT). Demographics of included studies are provided in Table 1.

Table 1: Table of demographics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Gaullier, 2007 (1)	Double blind, RCT	118	18-65	BMI 28-32 kg/m^2	Drug therapy, special diet or taking dietary substitutes for weight loss 2 weeks prior to the study, CLA consumption before the study, pregnant and lactating women, DM type II, HTN, renal disease, cardiac failure, malignant tumors, alcohol use, thyroid disease, drug abuse.	25	3-4 g/d of conjugated linoleic acid vs a placebo for 6 months
Watras, 2003 (2)	Double blind, RCT	48	18-44	BMI 25-30 kg/m^2	Drug therapy	8	3.2 g/d of conjugated linoleic acid vs a placebo for 6 months
Whigham, 2004 (3)	Double blind, RCT	64	18-50	BMI 27 – 35 kg/m^2	Unstable weight, no serious medical conditions, no interfering dugs, and not pregnant or lactating.	17	6g/day of conjugated linoleic acid vs a placebo for 5 months

OUTCOMES MEASURED

The outcomes measured in all three studies included both the change in body weight prior to and after treatment with CLA, and also the side effects in comparison to the treatment. Gaullier et al. measured body weight, BMI, vital signs, and complete blood work every three months. Whigham et al. had subjects follow up every two weeks for complete blood work and body composition by water dilution. Also every month, a body composition by BodPod® was performed monthly until the end of the study. Food intake and exercise diaries were submitted at each clinic visit. Watras et al. measured body weight monthly using Selinger's four-component model to calculate body fat mass: %BF = ((2.747/BD/Wt) – (0.7141(TBW/Wt)) + (1.146 * (TBM/Wt) – 2.0503) x 100, where %BF is percent body fat, BD is body density (kg/ l), Wt is body mass (kg), TBW is total body water (kg), and TBM is total body mineral (kg) calculated from a DXA scan. At months 0 and 6, blood chemistry work was performed on each subject.

Gaullier et al. defined an adverse effect as any unfavorable, unintended event. Adverse effects were divided into serious or non-serious. A serious adverse effect was defined as a life-threatening effect. Non-serious adverse effects were recorded every 3 months, while adverse effects were monitored continuously throughout the study. Whigham et al. used an adverse events questionnaire every two weeks to determine adverse effects. To measure adverse affects, Watras et al. used a 36 question questionnaire monthly throughout the study. Symptoms were grouped into four categories: cold or flu, general symptoms like nausea and headache, orthopedic symptoms such as joint and back pain, and emotional symptoms such as depression and irritability.

RESULTS

Table 2 compares placebo vs. CLA (3.4g/d) over a six month time period in the Gaullier et al. 2006 study. The comparative effects were made using a paired *t* test, comparing from baseline and at 6 months time. Categorical variables were analyzed using Fisher's exact test or a X^2 test. DEXA was used to determine the change of body fat mass (BFM) and comparisons between baseline and 6 months were performed using analysis of covariance. Compared to the placebo, CLA significantly decreased body fat mass (p=0.043), arm fat mass (p=0.027), leg fat mass (p= <0.001), and abdominal fat mass (p=0.027). However, the comparison between placebo and CLA for lean body mass (p=0.22) and bone mineral content (p=0.36) did not meet statistical significance. When comparing baseline to the six months period, it was found that BMI for all the subjects had a significant change (p=0.031) and when comparing the six month time period to only subjects who started with a BMI over 30kg/m^2, it was found that the reduction of weight by CLA was even more significant (p=0.020)

Table 2. Summary of Placebo vs. 3.4 g/day Conjugated Linoleic Acid (CLA) Comparing Body Fat Mass, Lean Body Mass (BFM), Bone Mineral Content (BMC), Arm Fat Mass (AFM), Leg Fat Mass (LFM), Abdominal Fat Mass (TFM), and Body Mass Index (BMI) Over a Period of 6 Months

Gaullier et al. 2006			
	Placebo	CLA 3.4g/day	p-value
BFM	-1.0 (kg)	+0.2 (kg)	0.043
LBM	-0.5 (kg)	+0.3 (kg)	0.22
BMC	0.0 (kg)	0.0 (kg)	0.36
AFM	-0.4 (kg)	-0.3 (kg)	0.027
LFM	-0.5 (kg)	+3.0 (kg)	<0.001
TFM	+0.3 (kg)	-0.2 (kg)	0.068
BMI	+0.1 (kg/m^2)	-0.5 (kg/m^2)	0.031
BMI $\geq$ $30kg/m^2$ [1]	+0.1 (kg/m^2)	-5.0 (kg/m^2)	0.020

[1]Subjects initially started with a BMI over $30kg/m^2$

Table 3 shows the results from the Watras et al. study. The primary outcome variable of was the change in body fat mass and that was measured using the four-component model. The *t*-test was used to determine differences between the groups at month 0 for all the variables. The results show that the 6 month loss in body fat was significantly greater with CLA compared to the placebo (p=0.02). The results also show a significant reduction in BMI with CLA compared to the placebo (p=0.05). There was no difference in the in the change in the fat-free mass (p=0.8) or abdominal fat mass (p=0.1).

Table 3. Summary of Placebo vs. 3.2g/day Conjugated Linoleic Acid (CLA) Comparing Body Weight, Body Mass Index (BMI), Fat-free mass (FFM), and Abdominal Fat Mass (Abd. FM) Over a Period of 6 Months

Watras 2006					
	Placebo		CLA 3.2g/day		
	Month 0	Δ (6-0 mo.)	Month 0	Δ (6-0 mo.)	p-value
Body weight (kg)	79.0 ± 10.9 *	1.1 ± 3.2	80.0 ± 9.1	-0.6 ± 2.5	0.02
BMI (kg/m^2) [1]	28.0 ± 2.2	0.4 ± 1.1	27.6 ± 1.8	-0.2 ± 0.9	0.05
FFM (kg) [2]	28.4 ± 5.0	0.7 ± 3.0	26.6 ± 5.5	-1.0 ± 2.2	0.8
Abd. FM (kg) [3]	7.5 ± 1.5	0.2 ± 1.2	6.9 ± 1.5	-0.2 ± 1.0	0.1

* All values are $\underline{x}$ + standard deviation

The Whigham et al. 2004 study used ANOVA models to analyze dated for body composition analysis. However, instead of displaying data, Whigham et al. stated that there were no significant changes overall in body weight or body fat between the CLA group and placebo after 12 months. The Whigham et al. study primarily focused on adverse effects of CLA.

Adverse events were noted throughout all three trials. Whigham et al. noted significantly lower frequencies of skin rash, depression, irritability/anger, hair loss, and infection in the CLA group vs. placebo. Watras et al. noted that the rate of cold and flu symptoms increased with CLA ($p = 0.02$) and placebo ($p < 0.0001$). There was a decrease in emotional symptoms such as anxiety and depression in the CLA group that was significantly different from the placebo group ($p = 0.04$). Gaullier 2006 et al. noted that there were similar adverse events in both groups ($p=0.85$). Most of the adverse events were related to the gastrointestinal or musculoskeletal systems. The numbers needed to harm (NNH) for the Gaullier et al. study was 20. Blood chemistries for safety profiles were also recorded in each study. In all three studies, levels of

change of glucose, insulin, ALT, and AST did not meet statistical significance between the placebo and CLA at the end of each study period as shown in Table 4.

Table 4. Summary of Change in Glucose, Insulin, ALT, and AST Levels in Studies

	Gaullier et al. 2006			Watras et al.2006			Whigham et al.2004		
	Δ (6-0 mo.) CLA 3.4/day	Δ (6-0 mo.) Placebo	p-value	Δ (6-0 mo.) CLA 3.2 g/day	Δ (6-0 mo.) Placebo	p-value	Δ (52 wks) CLA 6g/day	Δ (52 wks) Placebo	p-value
Glucose (mg/dl)	-0.48 ± 0.81*	-0.4 ± 0.74	0.40	2.8 ± 4.9	6.1 ± 5.9	NS[1]	†	†	NS
Insulin (μU/ml)	-3.2 ± 33.6	8.7 ± 72.3	0.93	2.1 ± 11.6	-0.6 ± 6.2	NS	1.78 ± 0.19	1.83 ± -0.20	NS
ALT (U/I)	-0.20 ± 13.64	†	0.92	-2.5 ± 20.7	6.6 ± 17.3	NS	†	†	NS
AST (U/I)	-1.14 ± 7.91	†	0.14	-4.2 ± 4.8	-3.0 ± 7.4	NS	†	†	NS

* All values are x + standard deviation
† Data not reported
[1]NS = Not significant, P >0.05

DISCUSSION

Conjugated linoleic acid has been a foremost ingredient on many dietary supplement pills. The articles reviewed studied CLA and its effect on adults over the age of 18, However, recent studies have shown that CLA may be a proven beneficial weight loss supplement for children. Racine et al. 2010 studied children ages 6-10, and found that after 7 months of 3g/d of CLA vs. placebo, subjects had a decrease in body fatness[7].

Although most studies have reported that CLA does not cause harmful, adverse effects, a study by Risérus et al. 2007 found that CLA may cause an increase in oxidative stress, which can

lead to insulin resistance. In a double-blind placebo-controlled trial, 60 men with metabolic syndrome received either CLA or a placebo for 12 weeks. It was found that CLA caused an increase in inflammatory markers and oxidative stress in men in the 12 week time. However, more studies are needed over a longer time period to truly establish CLA's effects on insulin resistance[8].

Limitations to all three studies were the lack of duration and number of test subjects used. Both the Gaullier et al. and Watras et al. studies only performed a six month study, while Whigham et al. study lasted a year. Longer studies are needed to determine long-term efficiency and adverse effects. Another limitation is that dietary supplements in the market are variable in quality and in the amounts of CLA they contain. The results of these studies may not be appropriate to generalize for all CLA products, due to the quality of the isomers used and the variable amounts of CLA the studies used, vs. the amounts found in weight loss supplements. The Watras et al. study had its own limitation, in that the subjects consisted of 80% overweight women. Because of this ratio, it may not be appropriate to generalize the data to men as well, considering the high percentage of women used in the study.

CONCLUSION

Based on blood work and reported adverse effects, the studies reviewed demonstrate that conjugated linoleic acid was found to be safe for human consumption. However, the Gaullier et al. and Watras et al. studies found that CLA did cause weight loss in subjects, while the Whigham study found no correlation between weight loss and CLA intake. Future studies should be designed to determine the correlation between CLA and weight loss. The studies in this review used age ranges from 18-64. However, more specific age studies should be conducted,

such as using ages 18-30, 30-40, etc. Also the studies did not use a set number of subjects per age range, instead many of the subjects were in their 50's and 60's. This alone can affect the results of weight loss, as it is harder to lose weight as an individual's age increases. In the future, studies should be designed either using an equal number of men and women, or a specific study should be conducted for men or women alone. Each study used different grams of CLA per day, however, a study should divide subjects and use different amounts, such as one group with 3g/day, another with 6 g/day, and a another on 9 g/day to truly see a difference in weight loss or adverse effects. Finally, the studies should be conducted over a longer period of time. Whigham had the longest study for a year, but two year studies should be conducted to truly determine long-term effects on weight loss and adverse reactions to CLA. Performing research with the adjustments in research studies will provide a more accurate answer to CLA's efficiency and safety.

REFERENCES

1. Vital Signs: State-Specific Obesity Prevalence Among Adults — United States, 2009. *CDC PMMR*. 2010;59:1-2.
2. McPhee SJ, Papadakis MA. Obesity. In: *Current Medical Diagnosis and Treatment.* 48th ed. New York: McGraw-Hill; 2009:1108-1100.
3. Padwal RS, Majumdar SR. Drug treatments for obesity: orlistat, sibutramine, and rimonabant. *The Lancet*. 2007;369(9555):71-77.
4. Gaullier JM, Halse J, Hoivik HO, et al. Six months supplementation with conjugated linoleic acid induces regional-specific fat mass decreases in overweight and obese. Br J Nutr. 2007;97(3):550-560.
5. Watras AC, Buchholz AC, Close RN, Zhang Z, Schoeller DA. The role of conjugated linoleic acid in reducing body fat and preventing holiday weight gain. Int J Obes (Lond). 2007;31(3):481-487.
6. Whigham LD, O'Shea M, Mohede IC, Walaski HP, Atkinson RL. Safety profile of conjugated linoleic acid in a 12-month trial in obese humans. Food Chem Toxicol. 2004;42(10):1701-1709.
7. Racine NM, Watras AC, Carrel AL, et al. Effect of conjugated linoleic acid on body fat accretion in overweight or obese children *Am J Clin Nutr*. 2010;91(5):1157-1164.
8. Riserus U, Arner P, Brismar K, Vessby B. Treatment With Dietary trans10cis12 Conjugated Linoleic Acid Causes Isomer-Specific Insulin Resistance in Obese Men With the Metabolic Syndrome *Diabetes Care*. 2002;25(9):1516-1521.