

PERSPECTIVES ON

Conjugated Linoleic Acid Research

Current Status and Future Directions

May 15-16, 2002

Lister Hill Auditorium

Bethesda, Maryland

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Conjugated Linoleic Acid Research



Contents

1 **AGENDA**

5 **SPEAKER ABSTRACTS**

**OVERVIEW OF CLA:
BIOCHEMISTRY AND METABOLISM**

6 The Origin of CLA

7 Documentation of CLA Intake in Humans;
What We Know and What We Should Know

8 Metabolism of Conjugated Linoleic Acid

9 Concepts for Development of an Analytical Method to
Determine CLA Composition in Foods, Dietary Supplements,
and Reference Materials

Contents

BIOLOGY/HEALTH EFFECTS

A. Obesity and Lipid Metabolism

- 10 Obesity and Lipid Metabolism: Body Fat
- 11 CLA Effects on Adipocytes: Mechanistic Considerations
- 12 Conjugated Linoleic Acid Isomers and Mammary Lipid Metabolism
- 13 PPARs as Potential Mediators

B. Cancer Effects

- 14 Toxicology Studies on Clarinol
- 15 Safety Assessment of Conjugated Linoleic Acid (CLA) Esters for the Use as Feed Additive in Pigs
- 16 CLA and Mammary Cancer Prevention Research
- 17 CLA Modulation of Mammary Stromal Differentiation Contributes to Its Chemopreventive Activity

C. Other Areas

- 18 CLA in Experimental Atherosclerosis
- 19 Conjugated Linoleic Acid's (CLA) Role in Immunity and Immune Related Disorders
- 20 Conjugated Linoleic Acid Reduces Fasting Glucose and is Inversely Correlated with Serum Leptin in Subjects with Type 2 Diabetes Mellitus
- 21 CLA and Bone Formation
- 22 Nutritional Regulation of Bacterial-Induced Colitis by Conjugated Linoleic Acid

Contents

HUMAN TRIALS/EFFICACY

- 23** Effects of CLA in Obese Subjects on a Weight Loss Diet:
Wisconsin Data
- 24** Clinical Studies on Metabolic Effects of Conjugated Linoleic Acid in Humans
- 25** Seroprotection: CLA Stimulates Antigen Specific Antibody Production in Humans

27 CHAIRPERSONS

31 SPEAKER LIST

37 ATTENDEE LIST

PERSPECTIVES ON

Conjugated Linoleic Acid Research



Agenda

Overall Chairs: *Clement Ip and Dale Bauman*

Wednesday, May 15th

OVERVIEW OF CLA: BIOCHEMISTRY AND METABOLISM

Pamela Starke-Reed, DNRC/NIH – Chair

7:00 am	Registration and Continental Breakfast	
7:45 am	The Origin of CLA	<i>Bauman</i>
8:20 am	Documentation of CLA Intake in Humans; What We Know and What We Should Know	<i>McGuire</i>
8:55 am	Metabolism of Conjugated Linoleic Acid	<i>Banni</i>
9:30 am	Concepts for Development of an Analytical Method to Determine CLA Composition in Foods, Dietary Supplements, and Reference Materials	<i>Yurawecz</i>
10:05 am	Panel Discussion	<i>Grinnari</i>
10:35 am	Break	

Agenda

BIOLOGY/HEALTH EFFECTS

A. Obesity and Lipid Metabolism

Paul Coates, NIH/ODS – Chair

10:55 am	Obesity and Lipid Metabolism: Body Fat	<i>DeLany</i>
11:30 pm	CLA Effects on Adipocytes: Mechanistic Considerations	<i>Pariza</i>
12:05 pm	Lunch	
12:55 pm	Conjugated Linoleic Acid Isomers and Mammary Lipid Metabolism	<i>Baumgard</i>
1:30 pm	PPARS as Potential Mediators	<i>Vanden Heuvel</i>
2:05 pm	Panel Discussion	<i>Mersmann</i>

B. Cancer Effects

John Milner, NIH/NCI – Chair

2:35 pm	Toxicology Studies on Clarinol	<i>O'Hagan</i>
3:10 pm	Safety Assessment of Conjugated Linoleic Acid (CLA) Esters for the Use as Feed Additive in Pigs	<i>Hasselwander</i>
3:45 pm	Break	
4:05 pm	CLA and Mammary Cancer Prevention Research	<i>C. Ip</i>
4:40 pm	CLA Modulation of Mammary Stromal Differentiation Contributes to Its Chemopreventive Activity	<i>M. Ip</i>
5:15 pm	Panel Discussion	<i>C. Ip</i>

Agenda

Thursday, May 16th

C. Other Areas

Deborah Applebaum-Bowden, NIH/NHLBI – Chair

7:45 am	Continental Breakfast	
8:30 am	CLA in Experimental Atherosclerosis	<i>Kritchevsky</i>
9:05 am	Conjugated Linoleic Acid's (CLA) Role in Immunity and Immune Related Disorders	<i>Cook</i>
9:40 am	Break	
10:10 am	Conjugated Linoleic Acid Reduces Fasting Glucose and is Inversely Correlated with Serum Leptin in Subjects with Type 2 Diabetes Mellitus	<i>Belury</i>
10:45 am	CLA and Bone Formation	<i>Watkins</i>
11:20 am	Panel Discussion	<i>Bassaganya-Riera & Houseknecht</i>
11:50 pm	Lunch	

Agenda

HUMAN TRIALS/EFFICACY

Beth Yetley, FDA – Chair

- | | | |
|----------------|---|-----------------|
| 1:00 pm | Effects of CLA in Obese Subjects on a Weight Loss Diet: Wisconsin Data | <i>Atkinson</i> |
| 1:35 pm | Clinical Studies on Metabolic Effects of Conjugated Linoleic Acid in Humans | <i>Vessby</i> |
| 2:10 pm | Seroprotection: CLA Stimulates Antigen Specific Antibody Production in Humans | <i>O'Shea</i> |
| 2:45 pm | Panel Discussion | <i>Kelley</i> |
| 3:15 pm | Break | |

3:30

OVERALL SUMMARY AND DISCUSSION

C. Ip & D. Bauman

Speaker Abstracts

The CLA in foods derived from ruminants relates to the biohydrogenation of unsaturated fatty acids by rumen bacteria and most of the work has involved dairy cows and milk fat. *cis-9, trans-11* CLA is the predominant isomer representing 75 to 80% of total CLA. This isomer is formed as an intermediate in the biohydrogenation of linoleic acid. Although rumen production is the source for a portion of milk fat CLA, the major source is endogenous synthesis. Between 70 to 95% of the *cis-9, trans-11* CLA in milk fat originates by endogenous synthesis via Δ^9 -desaturase from *trans-11* C18:1, another biohydrogenation intermediate. In ruminants, Δ^9 -desaturase activity is high in adipose tissue of growing animals, and in mammary tissue and adipose tissue of lactating animals; mRNA and protein for this enzyme are negligible in liver. The second most prevalent CLA isomer in milk fat is *trans-7, cis-9* and it originates almost exclusively from endogenous

synthesis involving Δ^9 -desaturase and *trans-7* C18:1 produced in the rumen. Other CLA isomers in milk fat, which are present in much lower quantities, originate from rumen biohydrogenation. Under certain dietary conditions, a portion of linoleic acid biohydrogenation in the rumen can involve an isomerization of the *cis-9* double bond to form *trans-10, cis-12* CLA. These diets are associated with a change in the rumen environment, an increase in milk fat content of *trans-10, cis-12* CLA, and a marked reduction in milk fat secretion. Overall, milk fat content of CLA is largely dependent on rumen outflow of *trans-11* C18:1 and tissue activity of Δ^9 -desaturase; both of these variables can be markedly affected by diet and vary substantially among individuals. Thus, by manipulating the diet and through genetic selection, the CLA content of foods derived from ruminants can be altered.

Because of the clear potential for various isomers of CLA to influence human health, documentation of dietary CLA in the human diet is of interest. Various methodologies have been utilized to quantify intake of CLA, including the use of disappearance data, dietary recalls, food frequency questionnaires, weighed food records and biochemical analysis of food duplicates. These methodologies all have limitations, although the analysis of food duplicates is considered the gold standard at this time. For example, accuracy of all of the indirect methods relies heavily on the accuracy of a database containing the CLA contents of commonly consumed foods. Although a substantial amount of work was conducted initially to document CLA in various foods, our database remains limited. Further, although a growing literature suggests that the various CLA isomers influence human health differently, very little data are published concerning the isomeric CLA contents of foods. None-the-less, researchers utilizing indirect methodologies have estimated CLA intakes in various locations including the United States, Australia, German and Finland; typical intakes are reported to range from 50 to 1000 mg/d. Using food duplicate methodology, we have also documented that “total CLA” intakes are 212 and 151 mg/d in adult men and women, respectively; c9,t11-CLA intakes were found to be 193 and 140 mg/d in men and women, respectively. Estimates by food duplicate methodology are consistently lower than those collected with food records.

Because of our interests in infant and child health, we have also documented CLA intakes in these groups. We and others have documented that human milk contains a variety of CLA isomers in relatively high concentrations, potentially resulting in quite high CLA intake by breastfed, but not formula-fed babies. More recently, we studied school-aged children (5-15 yr; n = 40) and documented total CLA and c9,t11-CLA intakes by weighed 3-d records. Data suggest relatively high intakes of CLA in this age group. No relationship between age and absolute CLA intake was found; relative to body weight, CLA intakes were highest in the youngest children. Interestingly, girls consumed significantly more CLA than did boys (184 and 158 mg/d, respectively). The physiologic consequences of CLA intake throughout the lifespan are currently not understood. However, early programming during fetal growth, infancy and childhood might decrease risk for chronic disease in later life. Thus, a better and more accurate understanding of CLA intakes and factors influencing CLA consumption throughout the lifespan might lend insight into what might be considered appropriate dietary recommendations for this potential nutrient. Further, this information is needed to better delineate which effects of CLA might be realized from dietary intake, and which effects can only be obtained from supplementation.

Among 28 possible conjugated linoleic acid (CLA) positional and geometrical isomers only the 9cis, 11trans and the 10trans, 12cis have been extensively tested for biological activities.

Both these CLA isomers have been shown to undergo elongation and desaturation processes similar to those occurring with linoleic acid, in a variety of animal species and also in humans, retaining the conjugated diene structure. Thus, CLA seems to interfere with linoleic acid metabolism, and thereby with arachidonic acid deposition, particularly in those tissues where CLA and some of its metabolites, conjugated 18:3 and conjugated 20:3 acid are preferentially incorporated such as adipose and mammary tissues because of their higher incorporation into neutral lipid. On the other hand, conjugated 20:4 is preferentially incorporated into specific phospholipids mainly phosphatidylinositol and phosphatidylserine.

In adipose and mammary tissues the metabolites content ranges from 5 to 15% of total CLA, and in plasma and liver from 10 to 30%. Other metabolites with 16 carbon atoms, conjugated 16:2 and 16:3, deriving most probably from peroxisomal beta oxidation of CLA and its metabolites respectively, have been detected. This suggests an efficient metabolism of CLA and its metabolites in peroxisomes

As a polyunsaturated fatty acid that gives rise to 20 carbon atoms metabolites, CLA metabolism may interfere with eicosanoid formation by different ways, 1) by decreasing arachidonic acid supply, 2) by interfering with lipoyxygenase and cyclooxygenase pathways, 3) by forming eicosanoid-like molecules which may then compete with regular eicosanoids.

Concepts for Development of an Analytical Method to Determine CLA Composition in Foods, Dietary Supplements and Reference Materials

Martin P. Yurawecz, Kim M. Morehouse
and Pierluigi Delmonte

*Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration*

Current qualitative and quantitative determination of conjugated linoleic acid (CLA) isomers in foods, dietary supplements and reference materials involves the complementary use of both GC, with FID or MS detection, and silver ion (Ag⁺) HPLC with UV detection. To date, the identification of CLA isomers has been performed by using Ag⁺ HPLC with GC confirmation, or visa versa. An internal standard was used to quantitate the total CLA by GC, and Ag⁺ HPLC quantitation was calculated from the GC data based on the type of isomer either c,c or t,t or c/t. This type of analysis, utilizing the GC data to quantitate the Ag⁺ HPLC data, was necessary because both the extinction coefficients and the absorbance

maxima for each type of c/t isomer are different. A procedure will be described that greatly improves both the identification and quantitation of CLA isomers based on their HPLC retention volumes relative to toluene, and the use of secondary internal standards containing well characterized UV chromophores (ϵ_{max} and $\epsilon_{\text{coefficients}}$). This will simplify the quantitation using Ag⁺ HPLC, which is the technique that provides the best separations.

Conjugated linoleic acid (CLA) has been shown to reduce body fat accumulation in several animal models. We have conducted several studies in AKR/J mice showing that CLA reduces body fat accumulation whether animals are fed a high fat or low fat diet, with no effect on food intake. One mechanism by which CLA reduces body fat is by increased energy expenditure, which is observed within 1 week of CLA feeding and is sustained for at least 6 weeks. The increased energy expenditure is sufficient to account for the decreased fat accumulation. We have observed increased fat oxidation but no decrease in *de novo* fat biosynthesis with CLA feeding. All of the early CLA studies were undertaken using a synthetic preparation containing approximately equal amounts of the major isomer found in beef and dairy (c9t11) as well as another isomer (t10c12) which is very low in natural

products. The Wisconsin group first showed, and we confirmed that the active isomer responsible for the reduced body fat accumulation is the t10,c12 isomer. The potential negative effects of CLA, namely increased liver weights and increased insulin levels were also in response to the t10,c12 isomer. We have shown that a dose of t10,c12 as low as 0.15% is effective in reducing body fat while animals were on either a low fat or a high fat diet. We have also demonstrated that CLA is effective in reducing body fat in older mice, who were already obese. All of the previous work had been done in young, growing animals, and these studies showed that CLA is effective in older animals as well, which would have implications in the use of CLA in humans. The published human studies with CLA have shown mixed results.

**CLA Effects on Adipocytes:
Mechanistic Considerations**

Michael W. Pariza

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Department of Food Microbiology and Toxicology
University of Wisconsin-Madison*

Conjugated linoleic acid (CLA) exhibits a number of seemingly disparate biological/physiological effects including inhibiting carcinogenesis at several stages in experimental animals, reducing atherosclerosis, reducing body fat gain, and enhancing immune function while reducing the catabolic effects of immune stimulation. The biochemical mechanisms that underlie these observations are emerging from research in a number of laboratories. These mechanisms originate with the isomers of CLA, in particular the *cis-9*, *trans-11* and *trans-10*, *cis-12* CLA isomers, both of which have been shown to exhibit biological activity. Emerging evidence indicates that these CLA isomers act both independently and in concert

to produce the multitude of biological/physiological effects that are attributed to CLA. CLA-induced reduction in body fat gain is an example of a single-isomer effect that is due specifically to the *trans-10*, *cis-12* isomer. There are two aspects to elucidating the biochemical mechanism(s) that underlie this observation: determining if *trans-10*, *cis-12* CLA acts directly or via a metabolite to regulate lipid accumulation in adipocytes; and identifying the signaling pathways through which *trans-10*, *cis-12* CLA (or its bioactive metabolite) act to control body fat gain *in vivo*. New findings that address these issues will be presented.

Abstract Text: Supplemental conjugated linoleic acids (CLA) reduce milk fat synthesis in lactating cows, sows and women. CLA effects are specific for fat as other milk components are unchanged. We have demonstrated effects on mammary lipid metabolism are the result of *trans*-10, *cis*-12 CLA, as similar amounts of exogenous *cis*-9, *trans*-11 CLA have no effect on milk fat parameters. Abomasal infusion of purified *trans*-10, *cis*-12 at a rate of 3.5 to 14.0 g/d decreases milk fat yield by 25 to 50%, respectively. The mammary gland is more sensitive to CLA than adipocytes as the amount of CLA required (0.016% of diet) to substantially reduce milk fat synthesis is much lower than needed (0.5 to 1.5% of diet) to reduce the body fat content in growing animals. Examination of the milk fat composition demonstrates CLA causes a reduction in secretion of all fatty acids, but those of *de novo* origin are more extensively affected. On a molar basis, ~80% of the decrease in milk fat yield can be explained by a reduction in fatty acids synthesized within the mammary gland. In addition, using substrate/product ratios as a proxy for the Δ^9 -desaturase it is evident that CLA inhibits this enzyme. Consistent with changes in milk fatty acid composition, we demonstrated *trans*-10, *cis*-12 CLA reduces mRNA expression of enzymes

(ACC, FAS & Δ^9 -desaturase) required for *de novo* fatty acid synthesis. Furthermore, mammary lipogenic capacity, as measured by labeled acetate incorporation into lipid, was dramatically reduced (>80%) when cows received exogenous *trans*-10, *cis*-12 CLA. At low doses *trans*-10, *cis*-12 CLA equally reduces the yield of *de novo* and preformed fatty acids. Consistent with this CLA decreases the expression of enzymes responsible for uptake and intracellular transport of preformed fatty acids (LPL & FABP), which largely explains how CLA decreases the milk fat content of lactating sows and nursing women, two species where utilization of preformed circulating lipids is the predominant source of milk fatty acids. In addition, *trans*-10, *cis*-12 CLA reduces the mRNA expression of enzymes involved in fatty acid esterification (GPAT & AGPAT). However, the amount of CLA required to reduce milk fat synthesis in lactating cows has little or no effect on circulating metabolites (NEFA, glucose & β -hydroxybutyrate) or hormones (insulin & leptin) associated with bioenergetics. It is thought that other specific CLA isomers (i.e. *trans*-8, *cis*-10 CLA) or conjugated trienes may alter milk fat synthesis but they have not yet been tested in pure form.

Conjugated linoleic acids (CLA) are a group of positional and geometric isomers of linoleic acid (LA). Interest in these dietary fatty acids stems from the fact, unlike LA, CLA is protective against cancer, atherosclerosis and diabetes in a variety of animal models and in some preliminary human trials. Despite the plethora of studies showing the beneficial properties of CLA, there is a paucity of mechanistic information on how this compound exerts its effects. Also, there has been little detailed exploration of how the various isomers differ in their biological effects. The tissue and isomer specific effects raise the possibility that CLA requires interaction with a cognate receptor to produce its response. We hypothesized that CLA causes its positive effects by regulating gene expression subsequent to binding to one (or perhaps several) fatty acid-regulated transcription factor(s). In particular, we have focused on nuclear receptors (NRs) implicated in fatty acid regulation of gene expression, the PPAR family (α , β/δ and γ). Each PPAR subtype has evolved to fulfill a different biological niche and are targets of important hypolipidemic and anti-diabetic drugs. All

three members of this receptor family are activated by CLA isomers, although their affinity for PPAR α is much greater than for β and γ . The ability to activate PPAR α may help explain CLA's effect on hepatic fatty acid metabolism. Since the biological role of PPAR β is not well established, it is difficult to determine if activation of this receptor may explain the health benefits of CLA. We have focused our recent attention on PPAR γ because of its beneficial role in diabetes, inflammation and cancer. Although CLA isomers are weak ligands for PPAR γ , we have shown that this receptor is essential for these fatty acids to regulate gene expression in the macrophage and in the adipocyte. The possibility exists that CLA isomers require metabolism to become an active PPAR γ ligand. Together, these studies have identified activation of PPAR γ as a possible mechanism by which CLA can regulate gene expression and ultimately result in its beneficial effects. This detailed molecular information on how CLA results in its health benefits in animal models may assist in determining the benefit of supplementation of CLA in humans.

Conjugated linoleic acid (CLA) is found naturally in foods such as dairy and meat products. In nature the c9, t11 isomer predominates. Commercial preparations contain a mixture of isomers, with c9, t11 and t10, c12 often occurring in equal proportions. In addition, the potential intake from commercial sources of CLA is higher than that from the diet. A program of toxicology studies was therefore conducted to confirm the safety of a preparation containing a mixture of CLA isomers.

Clarinol was tested in two *in vitro* mutagenicity assays and a 90-day repeat dose rodent study. Clarinol was non-mutagenic in both *in vitro* assays. In the repeat dose study, Clarinol was administered to Wistar (CrI: (WI) WU BR) rats as part of the diet for a period of

90-days. The material was tested at a dose level of 1%, 5% and 15% in a synthetic diet (AIN-93G). A high fat control diet containing 15% safflower oil was also tested in the study. In keeping with the findings from other studies on CLA, Clarinol was found to cause liver enlargement. The pathology data indicate that this is an adaptive effect that occurs only in female rats with high doses of CLA, and is reversible upon withdrawal of the test material. A No Observed Adverse Effect Level was identified in the study.

Safety Assessment of Conjugated Linoleic Acid (CLA) Esters for the Use as Feed Additive in Pigs

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Braun, J.; Hasselwander, O.; Kaesler, B.

BASF AG Ludwigshafen, Germany

CLA is a generic term describing different naturally occurring isomers of linoleic acid with 2 conjugated double bonds. The two primary CLA isomers have c9,t11 and t10,c12 configuration. Beneficial effects of CLA such as change in body composition, chemoprevention and improved insulin sensitivity have been reported in animals.

BASF is developing CLA for the use as feed additive in pigs at concentrations up to 0.5% of the finished feed. In order to assess the safety of CLA esters a series of toxicological and experimental animal studies was carried out. These comprised experimental toxicity studies, mutagenicity studies as well as a target animal safety study and efficacy studies in pigs. In addition, CLA effects on body composition and insulin sensitivity have been investigated in mice and rats, respectively.

Results from the available studies, which will be presented, indicate that CLA esters used as feed additive at concentrations up to 0.5% in animal feed are safe.

There is strong evidence that CLA is an effective anticancer agent in the animal model. Although a number of cancer sites have been shown to be protected by CLA, tumor development in the mammary gland appears to be particularly sensitive to CLA intervention. This may be due in part to the preferential accumulation of CLA in neutral lipid of adipocytes, which represent the predominant cell type in the mammary tissue. CLA stored in adipocytes could conceivably serve as a “paracrine factor” in regulating the growth of mammary epithelial cells. In the rat mammary epithelium, there are morphologically distinctive structures called terminal end buds (TEBs) which are present at the tip of some subtending tubules of the mammary tree. TEBs are the primary sites for the chemical induction of mammary carcinomas. We will present data showing that CLA is able to inhibit the formation of premalignant lesions from TEBs after exposure to a carcinogen. Clonal expansion of an early transformed pathology is the net result of cell proliferation minus cell death. Both of these pathways are regulated by a large number of genes whose protein products act as molecular switches in either a positive or negative manner. We will discuss some of our recent

work showing that CLA treatment leads to the modulation of a panel of biomarkers which are suggestive of a decrease in proliferation and an increase in apoptosis. Dairy products that are enriched in 9,11-CLA are of special interest to the food industry. Vaccenic acid, an intermediate in the biohydrogenation of linoleic acid in the rumen, is also high in cow’s milk. There is emerging data that mammals have the ability to convert vaccenic acid to 9,11-CLA via the Δ^9 -desaturase reaction. Studies evaluating the feasibility of using vaccenic acid as a precursor for the endogenous synthesis of 9,11-CLA in achieving cancer protection will be described. The desaturation and elongation of CLA in animal tissues have been well documented. This knowledge opens up a new avenue of research which is related to the question of whether the metabolism of CLA is essential for its anticancer activity. For scientific reasons, it is critical to delineate whether CLA or one of its metabolites, is the proximate effector molecule. Future research direction needs to focus on the signaling pathway of CLA and the molecular targets that are responsible for the anticancer effect of CLA.

CLA Modulation of Mammary Stromal Differentiation Contributes to It's Chemopreventive Activity

Margot M. Ip and Patricia A. Masso-Welch

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CLA has been shown to have marked chemopreventive activity in rat mammary carcinogenesis models. In part, CLA exerts this effect by acting directly on the mammary epithelium to inhibit DNA synthesis and stimulate apoptosis. The objective of our current studies has been to determine if CLA might also act indirectly, by modifying the mammary stroma. To examine this, we investigated the effect of CLA on a multipotent stromal-vascular cell (MSC) population which is present in the rat mammary gland, and which is able to acquire a fibroblastic, adipocyte or endothelial phenotype, depending on culture conditions (Zangani *et al*, Differentiation 64: 91, 1999). In these experiments, t10,c12-CLA was found to be a potent adipogenic factor, stimulating MSC to the adipogenic differentiation pathway even in the absence of exogenous hormonal supplementation; c9,t11-CLA was less effective. This effect of CLA was accompanied by a rapid loss in the DNA-binding activity of the PPAR γ /RXR α heterodimeric transcription factor complex, suggesting that PPAR γ may play a key role in initiating the recruitment of MSC into the adipogenic pathway. DNA-binding activity of other transcription factors examined was not decreased, demonstrating the

specificity of this response. Significantly, concurrent with MSC differentiation along the adipogenic lineage, there was a decreased ability of MSC to form micro-capillary networks *in vitro* on an EHS tumor-derived reconstituted basement membrane (RBM). This suggested that CLA might inhibit angiogenesis *in vivo*. To test this, mice were fed diets with or without CLA for 6 weeks, and then injected subcutaneously with an angiogenic gel substrate composed of RBM supplemented with β FGF and heparan sulfate. One week later, the RBM pellets were harvested and examined histologically. These studies demonstrated that functional angiogenesis (formation of red blood cell-containing vessels) was decreased by ~80%. CLA also significantly decreased serum and mammary gland concentrations of vascular endothelial growth factor (VEGF), and the mammary gland VEGF receptor, flk-1. In summary, the ability of CLA to modulate mammary stromal cell differentiation and decrease angiogenesis may contribute to its efficacy in inhibiting mammary carcinogenesis.

The effect of dietary CLA on experimental atherosclerosis has been studied in hamsters and rabbits. Hamsters fed 0.12% cholesterol and 1% CLA had significantly lower plasma cholesterol levels than controls and exhibited significantly less severe aortic sudanophilia. In rabbits fed a semipurified diet containing 0.2% cholesterol for 90 days, 1% dietary CLA inhibited atherosclerosis by 36 and 58% respectively in two experiments. Lower concentrations of dietary CLA also reduced severity of atherosclerosis. In one study, CLA at 0.1 or 0.5% of the diet reduced severity by 34 and 64% respectively. An anti-atherogenic effect has been observed in rabbits fed as little as 0.05% CLA. These studies were conducted using a mixture of the major CLA isomers (about 42-44% each of the c9,t11 and t10,c12 modifications). The individual isomers (fed as 0.5% of the diet) each have about the same effect on atherogenicity as does the mixture.

When 1% CLA was fed to rabbits bearing pre-established atherosclerosis it led to a significant regression of the pre-established lesions. In one study regression amounted to 31%, vs. 2% regression in the controls. In a second study the respective values for CLA and controls were -30% severity and +8% severity. Lower levels of dietary CLA were without effect in the regression experiments. A study of individual CLA isomers' effects on regression is in progress,

Conjugated Linoleic Acid's (CLA) Role in Immunity and Immune Related Disorders

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Dan Butz, Guangming Li

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CLA has been shown to reduce immune- and autoim-
mune-induced cachexia, type-1 hypersensitivity, and
increase the longevity of the autoimmune lupus mouse.
Mechanisms of these health benefits were not by
way of immune suppression, but altered cytokine and
eicosanoids production has been demonstrated.
CLA (cis 9, trans 11 isomer) was found to suppress
lipopolysaccharide (LPS)-induced tumor necrosis
factor both *in vitro* and *in vivo*. Resident peritoneal
macrophages from CLA fed BALBc mice also had
suppressed LPS-induced nitric oxide production.
While interleukin-4 (IL4) was decreased in stimulated
splenocytes from CLA (mixed isomers) fed mice, IL-2
was increased. These results would suggest that
lymphocytes from CLA fed mice favor a Th-1 cytokine
profile. A shift towards Th-1 cytokine profile could
explain reduced IgE production, previously reported, as
well as the decreased type 1 hypersensitivity reaction
in tracheal airways. Inherently linked to the CLA's
effects on immunological function is the eicosanoid
(prostaglandins and leukotrienes) pathway.

Conjugated Linoleic Acid Reduces Fasting Glucose and is Inversely Correlated with Serum Leptin in Subjects with Type 2 Diabetes Mellitus

Martha A. Belury, Ph.D., R.D.

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Seattle, Washington*

Conjugated linoleic acid (CLA) delays the onset of diabetes in the Zucker diabetic fatty (ZDF; fa/fa) rats (Biochem Biophys Res Comm 244: 678-682, 1998). In addition to normalizing impaired glucose in an oral glucose tolerance test, CLA (1.5wt%) significantly reduced epididymal fat mass and serum leptin levels. The data suggested that CLA was able to delay diabetes through a mechanism targeting adipose tissue in this experimental animal model. The objective of the present study was to elucidate the relationship of supplemental CLA to improvements in the management of type 2 diabetes mellitus. We conducted a double-blind randomized study in subjects with type 2 diabetes supplemented with CLA (8.0 g, 76% pure CLA; n= 11) or placebo (8.0 g safflower oil, n=10) daily for eight weeks. The supplements were 76% CLA containing approximately 37% c9t11-CLA and 39% t10c12-CLA. Dietary assessment of intake of energy or fat composition revealed no differences at baseline or week 8 for either treatment group. Supplementation with CLA significantly decreased fasting blood glucose ($P < 0.050$) and exerted a modest trend for decreasing fasting plasma insulin ($p < 0.100$). The strengths of the associations of plasma levels of CLA to changes in body weight and serum leptin were determined by quantifying correlation coefficients. Plasma CLA was inversely correlated, although not significantly, with a change in body weight ($r = - 0.3739$; $P < 0.100$) and significantly inversely correlated with a change in leptin

($r = - 0.4314$; $P < 0.050$). Because it appears that individual isomers of CLA may differentially alter body composition of experimental animals, we determined the relationship of the naturally occurring isomer of CLA in the diet, c9t11-CLA (or rumenic acid), to changes in body weight and serum leptin. In comparison to correlation coefficients for total plasma CLA to a change in body weight or serum leptin, correlation coefficients of the level of rumenic acid (c9t11-CLA) in plasma were reduced for body weight ($r = - 0.3230$, $P < 0.200$) and serum leptin ($r = - 0.3961$; $P < 0.100$). These findings indirectly suggest the alternative isomer, t10c12-CLA, may exert a more potent effect than c9t11-CLA on reducing body weight and serum leptin in subjects with type 2 diabetes. Because the reduced body weights were significantly correlated with reduced fasting blood glucose levels ($r = 0.4601$; $P < 0.050$), our study suggests the improvement in fasting blood glucose by supplemental CLA may occur through lowering body weights and/or altering body composition. Further work is needed to identify the role of CLA in improving insulin sensitivity, reducing body weight and altering mass and distribution of adipose tissue in humans. In addition, future studies should determine the optimal doses and isomeric mixtures of CLA required to aid in the management of type 2 diabetes mellitus in a longterm study.

Skeletal metabolism is controlled by cells of the bone and joint microenvironments through the actions of prostaglandins, cytokines, and growth factors involved in the local regulation of bone metabolism. New studies suggest that specific PUFA improve bone metabolism and reduce or control the risk for bone/joint diseases. The PUFA and to some extent conjugated linoleic acid (CLA) modulate eicosanoid biosynthesis in osteoblasts, alter biomarkers of bone formation, impact bone formation rates in rats, and influence gene expression during osteoblast maturation and matrix formation. The first published study on CLA and bone formation showed that 1% dietary CLA isomers depressed ex vivo PGE₂ production in rat bone organ culture, reduced serum IGF-I, and reduced bone formation rate in rat long bone. These responses were influenced by the dietary ratio of n-6/n-3 fatty acids. In a subsequent study, a lower dietary level (0.5%) of CLA was supplemented to diets containing moderate or high levels of PUFA (moderate or high n-6 PUFA oil blend) appeared to rescue bone formation rate in male rats. The dietary lipid treatments did not affect growth; however, CLA improved feed efficiency during the first six weeks of feeding. CLA isomers were found in all rat tissues analyzed and CLA content in neutral lipid was 5 to 10 times greater than that in the polar fraction. CLA lowered 18:1n-9 and total monounsaturated fatty acids while it increased 22:6n-3 and total n-3 in the polar fraction of liver and bone marrow. Arachidonic acid

(20:4n-6) was decreased in liver polar lipids by CLA but not in bone. In the neutral lipid fraction of most rat tissues analyzed, CLA treatment decreased 18:1, 20:2, 20:4n-6, 22:5n-3, 22:6n-3, total monounsaturated, total n-6, total n-3, and total PUFA, but increased saturated fatty acids. Rat serum osteocalcin level and bone specific alkaline phosphatase (BALP) activity was decreased in rats fed CLA. In contrast, rats given the diet containing a moderate level of n-6 PUFA relative to the high n-6 PUFA had a higher rate of bone formation in the tibia. In addition, the supplement of CLA appeared to be protective in supporting bone formation in rats given a higher level of n-6 PUFA. Studies in osteoblasts enriched with CLA isomers during proliferation, maturation, and mineralization indicate the CLA down-regulates COX enzymes and has variable effects on signaling proteins and gene expression. In other experiments, bone mineral content and bone mineral density measured by DEXA in ovariectomized rats was not improved by CLA supplementation alone. Our research on CLA isomers in rats and other mammals indicates that the actions of these isomers is dependent on the type of dietary fat, the balance of PUFA (dietary ratio of n-6/n-3 fatty acids), and may influence factors at the molecular level.

**Nutritional Regulation of
Bacterial-Induced Colitis by
Conjugated Linoleic Acid**

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Excessive intake of saturated fatty acids and/or linoleic acid favors the induction of an array of lipid mediators and cytokines enhancing inflammatory responses. Conversely, dietary supplementation with n-3 fatty acids or vitamin D ameliorates inflammation and autoimmune diseases. While it was well-accepted that conjugated linoleic acid (CLA) prevented diseases with a common inflammatory pathogenesis (i.e., cancer, diabetes, and atherosclerosis), no studies were available on the roles of CLA on mucosal inflammation. The present study aimed at investigating the anti-inflammatory actions and molecular mechanisms underlying the regulation of colonic health by CLA. It was hypothesized that colonic inflammation can be ameliorated by dietary CLA supplementation. To test this hypothesis, inflammation of the colonic mucosa was triggered by challenging pigs fed either soybean oil or CLA-supplemented diets with an enteric bacterial

pathogen (i.e., *Brachyspira hyodysenteriae*). Immunoregulatory cytokines as well as peroxisome-proliferator activated receptor- γ (PPAR- γ) mRNA expression was assayed in colonic lymph nodes and colon of pigs. Colonic mucosal lesions and lymphocyte subset distribution were evaluated by histology and immunohistochemistry. Supplementation of CLA in the diet prior to the induction of colitis decreased mucosal damage, maintained cytokine profiles (i.e., interferon- γ and interleukin-10) and lymphocyte subset distributions (i.e., CD4⁺ and CD8⁺) resembling those of non-infected pigs, enhanced colonic expression of PPAR- γ and attenuated growth failure. Therefore, CLA fed preventively prior to the onset of enteric disease attenuated inflammatory lesion development and growth failure.

**Effects of CLA in Obese Subjects
on a Weight Loss Diet: Wisconsin Data**

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Obesity is a chronic disease that is resistant to diet, exercise, and lifestyle modification treatments. Pharmacologic treatment is somewhat more successful, but safety and long term efficacy are not clear. Drug treatment must be long term because cessation of treatment invariably leads to weight regain. Conjugated linoleic acid (CLA) in growing animals reduces body fat and increases lean body mass vs control animals. Human trials show no effect or modest reduction in body weight or body fat with CLA compared to placebo. We did a randomized, double-blind, placebo-controlled trial in 80 obese subjects treated for 6 months with placebo or 2.7 gm of CLA/day. Characteristics were mean age 41.5 yr, mean wt 94.0 kg, and absence of severe illness, pregnancy, lactation, or interfering drugs. Subjects were asked to reduce customary intake by 500 kcal/d and to exercise for 30 min at least 3

times weekly. Body composition was assessed by underwater weighing. 71 subjects (41 F, 30 M) finished the 6 mo trial. CLA subjects lost 2.4 kg vs 2.2 kg for placebo. Fat mass declined by 1.3 kg and 1.0 kg, respectively. Fat free mass decreased by 1.1 kg and 1.2 kg, respectively. Laboratory variables did not differ between the groups. Side effects and adverse events were significantly fewer in the CLA group ($p < .05$). We conclude that CLA does not enhance weight loss or reduce body fat in obese subjects on a weight loss program, but that it appears to be safe and to reduce side effects during weight loss over 6 months. Additional studies are needed in humans with research designs comparable to the animal studies to determine if CLA prevents adipose tissue accumulation.

Clinical Studies on Metabolic Effects of Conjugated Linoleic Acid in Humans

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Conjugated linoleic acid (CLA) comprises a group of unsaturated fatty acid isomers with a variety of biological effects in experimental animal studies. CLA reduces body fat accumulation and has been ascribed significant effects on lipid and glucose metabolism, e.g. antidiabetic effects in obese Zucker rats. It has been suggested that the t10c12 CLA isomer is the active isomer as regards antiobesity and insulin sensitizing properties of CLA. The metabolic effects of CLA in humans in general, and isomer specific effects in particular, are not well characterized. We have in a series of controlled studies in humans investigated the effects of CLA (given as the commercially available mixture of isomers) and of the purified t10c12 isomer on anthropometry, lipid and glucose metabolism, on

markers of lipid peroxidation and on endocrine and proinflammatory factors. Preliminary results indicate that CLA may slightly decrease body fat also in humans, particularly abdominal fat, but there is no simultaneous improvement of lipid or glucose metabolism. Rather, the t10c12 isomer unexpectedly caused significant impairment of the peripheral insulin sensitivity as well as of blood glucose and serum lipid levels. In addition, CLA markedly elevated lipid peroxidation. Thus, the metabolic effects of CLA in humans seem complex and further studies, especially of isomer specific effects, are needed.

Seroprotection: CLA Stimulates Antigen Specific Antibody Production in Humans

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Considerable evidence exists that CLA enhances immune function in vitro- and in animal-studies. In this study, the potential of CLA to modulate the human immune system was investigated using the two main isomers in different ratios (50:50 and 80:20 of c9,t11:t10,c12 CLA, respectively). The humoral and cell mediated immune responses were investigated in humans supplemented with CLA (1.7g active isomers/day for 12 weeks).

Hepatitis B (Hbs) vaccination was used as an infection model to investigate the humoral and cell mediated immune response. Hepatitis B antibody titres were evaluated for each subject on day 0 and 2 weeks post initial vaccination and final booster. Mean serum Hbs antibody concentration at day 85 was twice as high for subjects consuming CLA 50:50 compared with the control or the 80:20 group. The seroprotection rate

(SPR, i.e. the number of subjects with anti-Hbs concentrations >10 IU/L compared to the number of subjects with titers <10 IU/L) was significantly higher (P=0.05) for the 50:50 group compared with the control or the 80:20 group. The cell mediated immune response was measured using the CMI multitest for "Delayed-Type Hypersensitivity" (DTH). Evaluation of the DTH responses on 7 recall antigens, at different time points showed no statistically significant differences in all groups.

This is the first study in humans that clearly demonstrates stimulation of the humoral immune (antibody) response by CLA supplementation as reflected by an increase of the SPR.

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