Metabolic effects of conjugated linoleic acid in humans: the Swedish experience\textsuperscript{1–4}

\textbf{Ulf Risérus, Annika Smedman, Samar Basu, and Bengt Vessby}

\textbf{ABSTRACT}
Conjugated linoleic acid (CLA) comprises a group of unsaturated fatty acid isomers with a variety of biological effects. CLA reduces body fat accumulation in animal models and has been ascribed significant effects on lipid and glucose metabolism. It has been suggested that the \textit{trans}-10,\textit{cis}-12 isomer is the active isomer with regard to antiobesity and insulin-sensitizing properties. The metabolic effects in humans are not well characterized. We have investigated and published the effects of CLA (given as the commercially available mixture and as the purified \textit{trans}-10,\textit{cis}-12 isomer) on anthropometry, lipid and glucose metabolism, and markers of lipid peroxidation. The results from those studies indicate that CLA might slightly decrease body fat in humans, particularly abdominal fat, but there is no effect on body weight or body mass index. There is no simultaneous improvement in lipid or glucose metabolism. Rather, the \textit{trans}-10,\textit{cis}-12 CLA isomer unexpectedly caused significant impairment of the peripheral insulin sensitivity as well as of blood glucose and serum lipid concentrations. In addition, CLA markedly elevated lipid peroxidation. Thus, the metabolic effects of CLA in humans seem complex, and further studies, especially of specific isomers and of longer duration, are needed. \textit{Am J Clin Nutr} 2004;79:1146S–8S.

\textbf{KEY WORDS} Conjugated linoleic acid, CLA, abdominal obesity, lipid peroxidation, metabolic syndrome

\textbf{INTRODUCTION}
Countries where there is a high intake of dairy fat in the population are characterized by a high prevalence of coronary artery disease\textsuperscript{(1)}. Dairy fat is rich in saturated fatty acids that are known to elevate the serum cholesterol concentrations\textsuperscript{(2)}, impair insulin sensitivity\textsuperscript{(3)}, and probably increase the risk of thrombus formation\textsuperscript{(4)}, thus increasing the risk of coronary artery disease. Somewhat paradoxically, we found that a high proportion of dairy fat in the diet seemed to be associated with a beneficial metabolic profile when studied in 70-year-old men\textsuperscript{(5)}. One reason for this finding could be that a high intake of milk fat is part of a healthy lifestyle in elderly men. An alternative possibility is that milk fat might contain some metabolically active (protective) component which could counteract the other, less desirable properties of dairy fat. An interesting compound in this context is conjugated linoleic acid (CLA).

CLA comprises a group of unsaturated fatty acid isomers, present in milk fat and meat from ruminants, with a variety of biological effects when tested in vitro or in experimental animals. CLA reduces body fat accumulation in animal models\textsuperscript{(6, 7)} and has been ascribed significant effects on lipid and glucose metabolism\textsuperscript{(8, 9)}. It has been suggested that the \textit{trans}-10,\textit{cis}-12 isomer is the active isomer with regard to antiobesity and insulin-sensitizing properties\textsuperscript{(9, 10)}. The metabolic effects in humans are, however, not well characterized.

The aim of our studies was to elucidate the metabolic effects of CLA in controlled studies in humans. In these studies we investigated the effects of the commercially available CLA product (a mixture of the 2 isomers \textit{cis}-9,\textit{trans}-11 and \textit{trans}-10,\textit{cis}-12 CLA in similar proportions) as well as purified preparations of the isolated isomers.

\textbf{SUBJECTS AND METHODS}
All studies were performed as controlled, randomized, double-blind parallel group studies with duration of 4–12 wk. The studies were approved by the ethics committee of the Medical Faculty of Uppsala University, and all data were obtained in accordance with the revised Declaration of Helsinki. CLA capsules were given as supplements containing 2.2–4.2 g/d of the CLA isomers, combined or in isolated form. The participants continued on their habitual diets, as monitored by dietary surveys before and during the studies. The adherence to the prescribed regimens was good, and no significant subjective or objective side effects were registered during the trials.

The effects of CLA were studied in 2 different groups of subjects. Initially, we studied a group of healthy women and men\textsuperscript{(11)}. The following studies\textsuperscript{(12, 13)} were performed in abdominally obese men with metabolic syndrome, because we considered this group to be a more suitable and sensitive target group for CLA supplementation. Also, this group is prone to use commercially available supplements.

\textbf{RESULTS}

\textbf{Effects of conjugated linoleic acid on body weight and body fat}

None of the studies showed any effects by CLA on body weight or body mass index (BMI). There were, however, indications of a

\textsuperscript{1} From the Unit for Clinical Nutrition Research, Department of Public Health and Caring Sciences, University of Uppsala, Uppsala, Sweden.
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\textsuperscript{4} Address reprint requests to B Vessby, Unit for Clinical Nutrition Research, Department of Public Health and Caring Sciences, University of Uppsala, PO Box 609, SE-75125 Uppsala, Sweden. E-mail: bengt.vessby@pubcare.uu.se.
certain reduction of the proportion of body fat (especially abdominal fat) by CLA and \textit{trans-10,cis-12} CLA. Thus, body fat decreased by 3.8% (\(P < 0.001\), paired \(t\) test) after 3 mo in a CLA-treated group of healthy men and women (11) with a borderline significant difference (\(P = 0.05\), unpaired \(t\) test) from the control group (−1.2%). Body weight, BMI, and sagittal abdominal diameter (SAD) were unchanged. SAD is suggested to be the best simple anthropometric measurement of visceral fat. After 4 wk of supplementation of abdominally obese men (12) there was a significant decrease in SAD in the CLA group (−2%; \(P = 0.003\), paired \(t\) test) compared with placebo (\(P = 0.04\), unpaired \(t\) test). A similar tendency was seen in a comparable group of men treated for 3 mo (13) with a reduction of SAD within both the CLA group (−3%) and the group given the purified \(10\text{r},12\text{c}-\text{CLA isomer (−3%). When compared with the control group (−1.5%), the difference between the groups did not quite reach statistical significance (\(P = 0.07\), ANOVA).}

The findings in our studies are well in line with findings of others, indicating a certain, but limited, effect of CLA on body fat without any effect on body weight or BMI (14). However, there seems to be no clear relation between body fat reduction and dosage or duration of supplementation.

\textbf{Effects of conjugated linoleic acid on lipid and glucose metabolism}

The commercially available CLA mixture seemed to have little, if any, effect on lipid and glucose metabolism in humans. If anything, there was a tendency to a slight impairment of the plasma lipoprotein profile with an increase of apolipoprotein B in the healthy men and women (11) and a reduction of HDL cholesterol (−2%; \(P < 0.05\), unpaired \(t\) test) in the obese men (13). A reduction of HDL cholesterol was also observed in some other (15, 16) but not in all (17) human studies that used a CLA mixture.

The \textit{trans-10,cis-12} CLA isomer caused a clear impairment of the metabolic profile when given to abdominally obese men (13). Thus, the HDL cholesterol concentration decreased significantly (−4%; \(P < 0.01\), unpaired \(t\) test) with a concomitant (nonsignificant) tendency to increased VLDL triacylglycerol concentrations. The blood glucose concentrations increased (4%; \(P < 0.001\), unpaired \(t\) test), and there was a significant reduction in insulin sensitivity (−19%; \(P < 0.01\), unpaired \(t\) test), measured as the insulin sensitivity index with the euglycemic clamp, in the men already experiencing insulin resistance. The results indicate isomer-specific metabolic actions of CLA, at least in abdominally obese humans.

\textbf{Effects of conjugated linoleic acid on antioxidant vitamins, lipid peroxidation, and inflammation}

CLA is easily oxidized, and it was suggested that increased lipid oxidation might contribute to antitumorigenic effects (18, 19). In a series of studies we investigated the effects of CLA on antioxidative vitamins and lipid peroxidation in vivo in humans. CLA induced highly significant increases of the urinary excretion of \(8\text{-iso-prostaglandin (PG)} 2\text{a, a major isoprostanes, and 15-keto-dihydro-PGF}_{2\alpha}(15\text{-K-DH-PGF}_{2\alpha}, a major metabolite of PGF}_{2\alpha}, as indicators of nonenzymatic and enzymatically induced lipid peroxidation in humans, respectively (20, 21). The magnitude of the increase of \(8\text{-iso-PGF}_{2\alpha}(3\text{-}5\text{-fold from basal concentrations) was generally 3\text{–}4\text{ times that of 15K-DH-PGF}_{2\alpha}. There was no effect on the plasma concentrations of malonaldehyde, and the concentrations of \(\alpha\)- and \(\gamma\)-tocopherol did not decrease (20, 21).

The increased lipid peroxidation was directly related to the CLA administration, and the lipid peroxidation parameters returned to basal concentrations 2 wk after cessation of CLA intake (20).

When evaluated separately in the obese men, it was clearly shown that the increase of lipid peroxidation was significantly more pronounced after the \textit{trans-10,cis-12} CLA isomer than after the CLA mixture, again indicating that the lipid peroxidation might, at least to some extent, be an isomer-specific effect of CLA (22). In this study there was also a significant increase of C-reactive protein (CRP) by 110% compared with placebo (\(P < 0.01\), unpaired \(t\) test) after supplementation with \textit{trans-10,cis-12} CLA. The changes of CRP were significantly associated with the changes of \(8\text{-iso-PGF}_{2\alpha}(22).}

\textbf{Insulin resistance, lipid peroxidation, and inflammation}

The individual changes of PGF\(_{2\alpha}\), but not of CRP, were significantly and independently related to the aggravated insulin resistance. The effect of \textit{trans-10,cis-12} CLA is a unique example of when an induced lipid peroxidation can aggravate insulin resistance and increase inflammation. The dietary content of \textit{trans-10,cis-12} CLA is very small, but CLA supplements usually contain \(\approx40\%\text{ }\textit{trans-10,cis-12}\text{ CLA. It cannot be excluded that consumption of these supplements on a long-term basis might have proatherogenic effects in humans with metabolic syndrome.}

\textbf{CONCLUSIONS}

CLA and specifically the isolated isomers are interesting model fatty acids for studies of the effects of (structural differences of) unsaturated fatty acids in humans. Today, there is no clear indication for human use of CLA concentrates. The possible importance of the small reduction of body fat after supplementation with the commercially available CLA products, without evidence of an associated improvement in the metabolic profile, has to be weighed against the apparent reduction of HDL cholesterol and an increased lipid peroxidation. The possible health consequences of prolonged treatment periods are at present unknown. Human supplementation with high doses of the \textit{trans-10,cis-12} CLA isomer should be avoided while awaiting further information on possible effects and side effects. However, it cannot be excluded that future studies could point to clinical applications, eg, as a result of antitumorigenic properties or as a tool to prevent weight gain. This possibility certainly requires more research to increase the understanding of the mechanisms behind the effects of CLA and specific CLA isomers on a molecular level. More controlled studies in defined populations are needed, as are controlled studies for comparisons of the effects of different and well-defined (mixtures of) isomers and human studies of longer duration to secure long-term effects and safety.

There was no conflict of interest.

\textbf{REFERENCES}

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