Nutrition 32 (2016) 166–173

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

Association of conjugated linoleic acid consumption and liver enzymes in human studies: A systematic review and meta-analysis of randomized controlled clinical trials

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ARTICLE INFO

Article history:
Received 29 April 2015
Accepted 14 August 2015

Keywords:
Conjugated linoleic acid
Alanine aminotransferase
Aspartate aminotransferase
Alkaline phosphatase
Systematic review
Meta-analysis

ABSTRACT

Objective: The aim of this study was to systematically review the association of conjugated linoleic acid (CLA) consumption in two forms of foods enriched or supplemented with CLA on serum liver enzymes in human studies.

Methods: We searched PubMed, Google Scholar, Cochrane Library, ScienceDirect, ProQuest, and Ovid up to January 2015. Studies that examined the effect of CLA supplementation or foods enriched with CLA on liver enzymes concentrations among healthy adults were included. The mean difference and SD of changes in serum liver enzymes between the intervention and control groups were used as effect size for the meta-analysis.

Results: The analysis demonstrated that CLA supplementation led to slight and nonsignificant decreases in alkaline phosphatase (ALP) levels (mean difference [MD] −0.216; 95% confidence interval [CI], −0.60 to 0.17; $P = 0.28$). CLA intake can nonsignificantly increase alanine transaminase (ALT) levels (MD = 0.107 U/L; 95% CI, −0.29 to 0.244; $P = 0.124$) and can significantly increase aspartate aminotransferase (AST) levels (MD = 0.171 U/L; 95% CI, 0.034–0.307; $P = 0.01$). Subgroup analysis based on CLA source showed that CLA supplementation or foods enriched with CLA did not significantly alter ALT levels. Subgroup analysis showed that CLA supplementation led to significant increases in AST levels (MD = 0.224 U/L; 95% CI, 0.071–0.376; $P = 0.004$). However, foods enriched with CLA did not have any significant effects on AST levels.

Conclusion: CLA supplementation was associated with a significantly increased circulating AST without any significant effect on ALP and ALT levels. Prospective studies are necessary to assess the clinical outcomes of the association between CLA and liver enzyme concentrations.

Introduction

Liver enzymes increase in different acute and chronic liver disorders. Chronic liver conditions such as nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD) are quite prevalent. They are characterized by liver fatty infiltration, inflammation, necrosis, and fibrosis with different degrees. NAFLD is now recognized as one of the most common causes of chronic liver disease worldwide; it is a global health concern with a prevalence rate of 20% to 30% in Western countries and 15% in Asian countries [1]. Laboratory measurements and assessments of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) are used

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http://dx.doi.org/10.1016/j.nut.2015.08.013
0899-9007/

to assess liver diseases [2]. Patients with NAFLD often are identified by asymptomatic elevation of liver enzymes, most frequently of serum ALT, and nonalcoholic hypertransaminasemia, in which viral or other causes of liver disease are excluded, has been used as a surrogate marker for NAFLD [3]. These enzymes most often are elevated in patients with liver disease and may reflect liver injury [4].

Several human studies demonstrated that liver damage and hepatic de novo lipogenesis might be affected by nutritional alterations such as consumption of a high-protein, high-fat diet, high-fructose, carbohydrate diet [5–7]. Other suggested that dietary conjugated linoleic acid (CLA) had beneficial effect on body fat, cancer, and cardiovascular disease; however, they also showed that CLA led to liver hypertrophy and hepatic steatosis. In animals, liver weight increased by 20–50% [8].

Trans-fatty acids (TFA) are categorized into two groups: industrial TFAs and ruminant TFAs. Industrial TFAs consist of hydrogenated vegetable oil and ruminant TFAs contain CLA and vaccenic acid, which are produced by rumen bacteria from monounsaturated and polyunsaturated fatty acids. Hydrogenate means to add hydrogen atoms to unsaturated sites on the carbon chains of fatty acids by heating vegetable oils in presence of metal catalyst and hydrogen. During industrial hydrogenation, trans-double bonds are formed along the fatty acid molecules from position 6 and higher. For fatty acids with 18 carbon atoms, a peak concentration of trans-double bonds is found in position 9, as elaidic acid, with a Gaussian distribution of fatty acids with the trans-double bond in the other positions. The bacterial desaturation of polyunsaturated fat from grass and vegetables in the rumen also produces trans-double bonds all over the fatty acid molecules, but with a distinct preference for the double bond in position 11 of the 18 carbon fatty acids, as vaccenic acid [9]. CLA refers to a class of positional and geometric conjugated dienoic isomers of linoleic acid. Two main isomers of CLA are cis-9, trans-11 (c9, t11) CLA, and trans-10, cis-12 (t10, c12) CLA [10–12]. Dairy products, such as milk and cheese, as well as ruminant meats, such as beef and lamb, are natural sources of CLA. CLA can be synthesized naturally from rumen bacteria or by bioconversion of vaccenic acid in mammary gland of ruminants as well as partial hydrogenation of linoleic acid produces CLA industrially [9]. Commercial CLA is accessible as supplements that provide beneficial health effects [13,14]. Previous studies have documented that CLA has anticarcinogenic, antiatherogenic, and immune modulation benefits that may change body composition [14].

It has been documented that the effect of CLA on liver enzymes might depend on different forms of CLA, as natural foods enriched with CLA and CLA supplements, which have various effects of liver enzymes. However, different types of CLA isomers and their various doses have led to inconsistent results in various studies [12]. Therefore, it is necessary to summarize these controversial findings.

The present study aimed to systematically review the association of CLA consumption in two forms of foods enriched with CLA or CLA supplementation on liver enzymes in human studies.

Methods

Literature search

We searched PubMed, Google Scholar, Cochrane Library, ScienceDirect, ProQuest, and Ovid up to January 2015, using the following keywords: MeSH and non-MeSH terms: “cis-9, trans-11-conjugated linoleic acid” [Supplementary Concept], “trans-10,cis-12-conjugated linoleic acid” [Supplementary Concept], “conjugated linoleic acid” [tiab], “CLA” [tiab] in combination with “Non-alcoholic Fatty Liver Disease” [Supplementary Concept], “Fatty Liver” [Mesh], “fatty liver” [tiab], “non-alcoholic steatohepatite” [tiab], “non-alcoholic steatohepatitis” [tiab], “NASH” [tiab], “NAFLD” [tiab], “non-alcoholic fatty liver disease”[tiab], “non-alcoholic fatty liver disorders” [tiab], “liver fat” [tiab], “steatosis” [tiab], “ALT” [tiab], “AST” [tiab], “ALP” [tiab], “APT” [tiab], “aminotransferase” [tiab], and “liver enzymes” [tiab]. We searched without any restriction for study design, time, and language. Additionally, the reference lists from related retrieved articles were checked to find undetected desirable studies. All randomized controlled clinical (RCTs) that investigated effects on liver enzymes of CLA intake, either in the form of CLA supplementation or enriched or natural foods containing CLA, were selected. Two authors (SM and SMDR) separately screened titles and abstracts to find potentially relevant trials for the full review. Data were analyzed by MM. Any discrepancies regarding data extraction, study quality, or applied the inclusion criteria were resolved by discussing with RK and MHB.

Inclusion criteria

Studies were included in the meta-analysis if they met all of the following criteria:

1. RCT in design;
2. Human study;
3. Healthy adult participants without any disorders;
4. Intervention done by using CLA supplements or CLA-enriched foods; and
5. Assessment of serum AST, ALT, and ALP concentrations were used as outcome variables.

The study selection process is illustrated in Figure 1.

Exclusion criteria

We excluded animal studies, studies with patient participants (e.g., diabetic patients), studies on non-adult age groups, non-RCT studies, trials in which the intervention group received a mixture form of CLA (i.e., CLA with amino acids), and studies without complementary data or without placebo group. Moreover, experimental in vitro or in vivo studies were excluded. Finally, among 4825 articles found in the first search, 13 eligible RCTs were entered into our study.

Quality assessment

The quantitative 5-point Jadad score was used to assess the quality of the relevant studies based on randomization, concealment of the treatment allocation, blinding, completeness of follow-up, and use of intention-to-treat analysis. One score was allocated for each item with a possible score of 0 to 5 (highest level of quality) [15]. Studies with higher scores were considered to have better quality.

Data extraction

We extracted data including the last name of the first author, publication year, country of population, number of individuals in intervention and control groups, duration of intervention, age, sex, form, and dose of CLA and placebo, and mean and SD of change in serum ALT, AST, and ALP levels in each intervention and placebo group. Three studies [12,16,17] reported the mean with SE and we calculated SD values from SE and number of participants in each group. We calculated correlation coefficient with using eight articles that reported mean change ± SD, mean ± SD before and after intervention for ALT, six articles for AST, and 2 articles for ALP levels, and used them to calculate the mean changes and their corresponding SDs for other studies. Two studies conduct compared the effects of three doses of CLA supplement: 6.4 g/d [18] and 6.8 and 3.4 g/d [19] with placebo in their studies, therefore we extracted two effect sizes from these studies, and included them as two separate studies in meta-analysis. Two forms of CLA including 4.5 g/d CLA-free fatty acid (FFA) 80% (3.6 g active isomer c-9 t-11 and t-10 c-12) and 4.5 g/d CLA-triacylglycerol (CLA-TG) 76% (3.4 g active isomer c-9 t-11 and t-10 c-12) have been investigated [20]. We extracted two effect sizes from this study and included them in our meta-analysis as two separate studies. Additionally, two forms of CLA including CLA-FFA and CLA-TG were also previously investigated [21]; therefore we extracted two effect sizes from this study. In another study [12], participants were assigned to two categories of body mass index (BMI): <30 kg/m^2 and >30 kg/m^2 in both CLA and placebo groups; therefore we extracted two effect sizes from this study, as well. One study [22] had a crossover design, and we extracted the data of placebo-CLA group and CLA-placebo group separately.

Statistical analysis

The mean differences (MDs) with 95% confidence interval (CI) for the ALT, AST, or ALP levels in healthy adults were calculated for the CLA consumers and