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Review

Biological effects of conjugated linoleic acids supplementation

J. Oleszczuk¹, L. Oleszczuk¹, A.K. Siwicki², E. Skopińska-Różewska^{3,4}

¹ 1st Medical Division, Medical University of Warsaw, Żwirki I Wigury 61, 02-004 Warsaw, Poland

² Department of Microbiology and Clinical Immunology, University of Warmia and Mazury, Oczapowskiego 13, 10-957 Olsztyn, Poland

³ Department of Microwave Safety, Military Institute of Hygiene and Epidemiology, Szaserów 128, 04- 349 Warsaw, Poland

⁴ Pathology Department, Medical University of Warsaw, Chałubińskiego 5, 02-004 Warsaw, Poland

Abstract

Conjugated linoleic acids (CLA) are a group of polyunsaturated fatty acids (PUFA) with a single pair of conjugated double bonds. The major natural CLA isomer is 18:2 cis-9, trans-11 (c9, t11) linoleic acid, or ruminic acid (RA). Chemically synthesized CLA is also available, mostly as a mixture of RA and 18:2 trans-10, cis-12 (t10, c12) isomers in equal amounts (50:50). Consumption of ruminant meat (beef and lamb) and dairy products (milk and cheese) is the main source of dietary exposure to CLA. Despite numerous studies on animal and human models (tumorigenesis, obesity, immune response) it has not been established whether additional supplementation of CLA is of benefit. Moreover, some studies, conducted both in animals and in humans, reveal that CLA isomers may induce insulin resistance. Presently, balanced diet rich in CLA from natural sources is recommended. The purpose of this review was to sum up the results available in the literature.

Key words: Conjugated linoleic acids, tumors, immune response, obesity, insulin resistance

Introduction

Conjugated linoleic acids (CLA) are a group of polyunsaturated fatty acids (PUFA) with a single pair of conjugated double bonds. There are positional and geometric isomers of CLA (Kelly 2001). Natural CLA are produced in the rumen of cattle in the process of bacterial fermentation of linoleic acid as well as by Δ^9 -desaturation of trans-11-octadecanoic acid by *Butyrivibrio fibrisolvens*. Consumption of ruminant meat (beef and lamb) and dairy products (milk and cheese) is the main source of dietary exposure to CLA

(0.4% – 1% of total lipids, respectively) (Wang and Jones 2004). The variation in content of CLA is attributed to 7 different farm management schemes and various feeding practices as the concentration of CLA in meat or dietary products reflects directly the intake of these PUFAs in animal's diet (Kelly 2001). If cows are allowed to pasture feed naturally, or their diet is supplemented with corn oil, sunflower oil, fish oil or algae, more CLA is observed in meat and in the fat of milk products (Lin et al. 1995, French et al. 2000). Several studies show that grass-based diets elevate precursors for vitamin A and E, as well as antioxidants

such as glutathione and superoxide dismutase activity, as compared to grain-based diets (Daley et al. 2010). The inclusion of tannins in diets has been shown to improve milk yields and to increase CLA concentrations in ruminant-derived foods (Patra and Saxena 2011).

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Interest in CLA began with an evidence of its anticancer effects and has further broaden to weight loss, alteration of body composition as well as diabetes, hypercholesterolemia, hypertension and enhancing immune function (Bhattacharya et al. 2006, Stachowska 2008).

All of the described effects of CLA are caused by two isomers: c9, t11-CLA and t10, c12-CLA. In some cases an effect is produced by one of these isomers acting alone, in other cases the isomers act together. The purpose of this review is to summarize some effects of CLA supplementation reported in the literature.

CLA and cancer

The role of CLA in inhibiting tumour growth and/or its metastatic potential is ambiguous. In addition, the exact mechanism of anticancer CLA potential remains unclear. Some evidences demonstrate it might be associated with inhibition of the angiogenesis. Inhibitory effect of CLA on cutaneous angiogenesis induced in mice by syngeneic sarcoma cells was reported (Sommer et al. 2002). On the contrary, plant-derived linoleic acid (LA) presented stimulatory effect on angiogenesis and tumor growth (Sommer et al. 2001). Other authors demonstrated inhibitory effect of CLA on new vessels growth in the mammalian brain (Sikorski et al. 2008). It might be connected with depression of growth factors secretion. Dietary CLA decreased serum levels of vascular endothelial growth factor (VEGF) (Bhattacharya et al. 2006, Stachowska 2008). Moon et al. (2003) have found that CLA decreased bFGF – induced endothelial cell proliferation and DNA synthesis *in vitro*.

Interfering with components of the cell cycle might be of benefit in tumour management (CLA inhibits level of the cyclins D and A, and up-regulates p53 expression) (Kelley et al. 2007, Stachowska 2008). CLA antitumor action is also attributed to alteration of lipid peroxidation, eicosanoid metabolism and gene

expression (Kelley et al. 2007). All of those are, however, only possible, not well defined, mechanisms. Recently, Erickson and Hubbard (2010) have found that CLA and n-3 fatty acids reduced the proliferation of, and had increased toxicity towards, mammary tumor initiating stem cells.

When analyzing CLA antitumor activity it is important to distinguish some discrepancies between animal and human models, as in the latter the results tend to be various (Kelley et al. 2007, Plourde et al. 2008, Stachowska 2008).

Studies in animal models report that CLA inhibits chemically- induced tumors of the mammary gland, skin, colon, as well as peritoneal metastasis of human gastric and colon cancer cells in mouse and rat models (Kuniyasu et al. 2006, Sakai et al. 2006, Stachowska 2008, Shiraishi et al. 2010). Interestingly, the inhibition of tumorigenesis is dependent upon the dietary concentration of CLA mixtures (0.05-1%). However, further increase in intake of CLA above 1% of total fats does not increase its anticancer activity (Kelly 2001). The timing and duration of CLA feeding also seems to play an important role (Kelly 2001). The results of studies conducted in humans are far less conclusive. Dose- and time-dependent apoptotic effect of t9, t11 on human colon cancer cell lines has been reported (Beppu et al. 2006). Koronowicz et al. (2009) described that both c9 t11 and t10 c12 isomers suppress the proliferation of mammary cancer cell lines. However, Larsson et al. (2009) concluded that there is no evidence of protective effect of CLA against breast cancer. In addition, Ip et al. (2007) described that in mice over-expressing erbB2, t10 c12 supplementation stimulated tumor growth and development alongside with its metastasis.

It is worth mentioning that CLA mixtures originating from ruminant products have higher antiproliferative potency towards tumor cells than pure synthetic preparations (De La Torre et al. 2007). Therefore, it might be the reason of inconsistent results of CLA effects reported in the literature. Also the dose, isomers and their proportion used in the studies vary significantly. In addition, CLA is claimed to cause a weight loss, which is an important issue in patients with cancer, making CLA supplementation even more controversial subject (Rastmanesh 2011). Epidemiological studies on CLA intake related to breast and prostate tumorigenesis are not conclusive (Heinze and Actis 2012).

In conclusion, the role of dietary conjugated fatty acids (CFA) on cancer is still controversial. Multi-potent effects of CLA supplementation with many isomers in various proportions have been assessed in both animal and human models; however, the results remain ambiguous.

Recently, cancer chemopreventive ability of another group of conjugated fatty acids, conjugated linolenic acids (CLN) was described (Hennessy et al. 2011). They occur in higher quantities than CLA in natural products. Preclinical animal studies have indicated that feeding with CLN resulted in inhibition of colorectal tumorigenesis (Tanaka et al. 2011).

There is general agreement that hydrogenated vegetable oils may induce adverse health effects, including atherosclerosis and cancer. Surprisingly, Jung et al (2011) showed, that selectively hydrogenated soybean oil, rich in CLA, exerts strong anti prostate cancer activities, *in vivo* (rats) and *in vitro* (human prostate carcinoma cell lines).

CLA and immune response

Numerous publications demonstrate that CLA has the ability to modify immunity by influencing production of soluble factors and mediators of inflammation in both human and animal models (Kelly 2001, Bhattacharya et al. 2006). It has been reported that CLA up-regulates the humoral function by increased IgG, IgM and IgA production of spleen lymphocytes in a dose – dependent manner and reduces macrophage function by decreasing synthesis of inflammatory mediators and/or inflammatory enzymes (O’Shea et al. 2004). CLA also reduces IgE (as well as PGE2 and IL-12) which plays a crucial role in type-I allergic reactions (Sugano et al. 1998). Yamasaki et al. (2003) found that the t10, c12 isomer is responsible for CLA effect on immunoglobulin production. In pigs CLA supplementation had little effect on their immune function and blood chemistry variables (Wiegand et al. 2011). Ramirez-Santana et al. (2011) observed enhancement of antibody synthesis and lowering the proliferative ability of splenocytes in rats by feeding cis-9, trans-11 CLA during early life.

CLA decreases production of proinflammatory cytokines, mainly tumor necrosis factor alpha (TNF alpha) and interferon gamma (IFN gamma) that play a central role in pathogenesis of many chronic immunopathologies. The latter has been implied in inflammatory bowel disease (O’Shea et al. 2004, Basaganya-Riera and Hontecillas 2010). Linoleic acid and cis-9, trans-11 CLA isomer had no detectable effects on lipopolysaccharide (LPS)-induced TNF alpha production in cultured bovine blood. However, trans-10, cis- 12 CLA isomer attenuate LPS-induced TNF- alpha production by bovine immune cells (Perdomo et al. 2011).

Protective role of ruminant fatty acids against the development of atopic manifestations in animal and human studies was reported (Thijs et al. 2011).

CLA decreases the innate immune response by diminishing the activity of monocytes, macrophages and natural killers cells and lowering prostaglandins and leucotriens production (O’Shea et al. 2004). CLA dietary supplementation also improves antigen-specific adaptive immune response to viral and bacterial antigens. It seems to be of benefit especially to immunocompromised patients, where the response is slow or insufficient. Albers et al. (2003) suggest CLA might be useful as an oral adjuvant in vaccination in these cases as well as in elderly patients. However, this necessitates further evaluation.

There is also a complementary hypothesis that CLA might alter immune function by interaction with peroxisome proliferator-activated receptors (PPARs) which regulate the expression of genes responsible for energy balance and immunity as CLA isomers are potent modulators of PPARs (Moya-Camarena et al. 1999, Perdomo et al. 2011).

The exact mechanism of action of CLA on immunity is not clear, however, there is no doubt about the effect on innate and adaptive response.

CLA and body composition

It has been claimed that CLA modulates body composition possibly by decreasing energy intake (suppressing appetite), increasing energy expenditure in white adipose tissue, muscles, and liver tissue, suppressing lipogenesis or adipogenesis, stimulating lipolysis or delipidation, and apoptosis via adipocyte stress, inflammation, and/or insulin resistance (Kennedy et al. 2010). CLA supplementation decreases adipose mass and increases bone mass in mice, probably through modulation of nuclear receptor peroxisome proliferator-activated receptor gamma activity (Ing and Belury 2011).

A mixture of CLA isomers or t10, c12 alone reduce adiposity in most animal models, especially in rodents, but has been shown to be effective only in some human studies. Potential reasons for these discrepancies include the dosage administered and age, body weight, body fat, or metabolic status of the subjects (Wang and Jones 2004, Silveira et al. 2007, Kennedy et al. 2010). Dosage among species vary considerable, as in rodent studies usually approximately 20 times more CLA/kg body weight is applied in comparison to human studies. Moreover, the duration of the supplementation effect is arguable as some authors claim it stops immediately after withhold of the CLA intake (Kennedy et al. 2010). Therefore more human trials are required before CLA can be recommended for improving body composition, especially in reducing fat mass.

CLA and lipids

Atherosclerosis is an inflammatory disorder characterized by the accumulation of lipids and their metabolites in the artery wall. CLA that originate from the human diet have demonstrated anti-atherogenic properties in several experiments. There are many contradictory results of numerous studies run on animal models (rats, hamsters, mice, rabbits) with regard to CLA effect on lipid profile when taking into consideration cardiovascular prophylaxis. Most authors agree that if there is any beneficial effect on lipid profile, t10, c12 is the active isomer (Evans et al. 2002). It was recently shown by Stachowska et al. (2010) that only t-10, c-12 CLA isomer triggered delipidation of macrophages (decreased triacylglycerols concentration). Although there have been very few human studies that have evaluated the effects of CLA or individual isomers on risk factors for cardiovascular health, considerable variations between the results have been found. Benito et al. (2001) reported that there was no change in plasma lipid or lipoprotein levels after intake of 3.9 g CLA/day containing 11.4% of c9, t11 isomer and 14.7% of t10, c12 isomer. Smedman and Vessby (2001) showed that intake of 4.2 g CLA/day for 12 weeks did not affect serum lipid or lipoprotein concentrations. No effect on serum TG, TC, and HDL-C was again reported by Petridou et al. (2003) when they studied the effect of supplementation of 2.1 g CLA/day for 45 days in non-obese young sedentary women.

Interestingly, CLA supplementation affects not only plasma lipid profile but also has an adverse effect on fat synthesis during established lactation in cows. It reduces the fat content and shifts the fatty acid composition (Perfield et al. 2002). The same phenomenon was observed in rats, where CLA decreased TG concentrations in milk resulting in impaired growth and increased mortality of the suckling pups. Milk fat content was also significantly lower during CLA supplementation in breastfeeding women. Therefore it should not be consumed during lactation (Masters et al. 2002).

CLA and safety

In rats which were fed with control diet or supplemented diet containing 1.5% CLA, there were no adverse effects observed (Scimeca 1998). CLA supplementation in mice significantly decreased body fat mass with symptoms of lipoatrophic diabetes and hepatomegaly. According to Stout et al. (2011) CLA can initiate in mice the pathophysiology responsible

for hepatic insulin resistance. Studies in humans showed that both t10, c12 and c9, t11 isomers may decrease insulin sensitivity in humans at risk for cardiovascular diseases (Risérus et al. 2004a, Risérus et al. 2004 b).

A number of human clinical trials that relate to safety and efficacy were also conducted, in which no adverse effects were determined. However, some concerns have been raised about the potential safety of CLA for humans, because of the induction of fatty liver, insulin resistance, and lipodystrophy in mice and rats fed CLA or trans-10 cis-12 isomers-supplemented diets, and in some human trials the induction of enhanced C-reactive protein, lipid peroxidation, unfavorable changes in serum lipids, and reduced milk fat (Pariza 2008, Gudbrandsen et al. 2009, Vyas et al. 2012). Bearing in mind inconclusive results of studies analyzing CLA supplementation it is questionable whether intake is indicated. Moreover, there is no agreement on recommended dosage of CLA, but 3 grams per day seem to be most favourable (Kelly 2001). CLA supplementation in pregnancy is not recommended (Oleszczuk et al. 2011).

Conclusions

It is difficult to state whether CLA supplementation should be recommended. Apart from its doubtful biological effect, economic reasons should also be taken into consideration as synthetic isomers are less potent than natural ones, and sometimes might be harmful. Moderate consumption of lean red meat is unlikely to increase risk for cardiovascular disease or colon cancer. Since high prices of beef might be discouraging, cheese and milk products seem to be affordable. Thus one should rather eat a balanced diet rich in all ingredients rather than buy synthetic substances with debatable effects (McAfee et al. 2010).

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