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Linoleic Acid, Vegetable Oils & Inflammation

by Kevin L. Fritsche, PhD

Despite the consistency of favorable recommendations regarding dietary LA, the possibility that this fatty acid contributes to excess inflammation has received considerable attention.

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Abstract

Should we listen to warnings that linoleic acid (LA) promotes inflammation and that Americans would be healthier if they restricted their intake of LA (i.e., vegetable oils)? A recently published systematic review of 15 clinical trials failed to find any support for the "diet LA causes inflammation hypothesis." These findings support current recommendations that a diet with 5 to 10 energy percentage from polyunsaturated fatty acids, such as LA, is healthful and appropriate for most Americans.

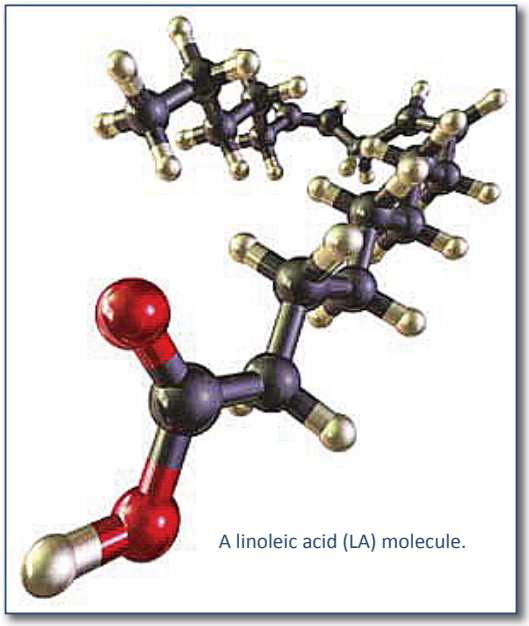
Introduction

On average Americans consume more than 40 grams (~3 tablespoons) of vegetable oil each day. Vegetable oils, such as those from soy, corn, or canola, are rich in linoleic acid (LA), an omega-6 fatty acid and an essential nutrient. Omega-3 fatty acids are also essential nutrients that can be obtained from soy, canola and flaxseed oils as well as certain cold-water fish, such as tuna, salmon, and herring. The relationship between and among the various members of these two families of essential nutrients has been the subject of much research and controversy. In this article, the focus will be on LA, from which all other omega-6 fatty acids can be derived.

The effects of dietary fats on cardiovascular disease (CVD) and other chronic health conditions have long been an important consideration in the development of dietary guidelines in the United States and around the world. The 2010 Dietary Guidelines for Americans[1] recommend that monounsaturated and polyunsaturated fats be substituted for saturated fats in the diet. There is currently much consistency among recommendations from government and professional organizations that both omega-6 and omega-3 classes of polyunsaturated fatty acids (PUFA) are desirable, and that LA as well as omega-3 PUFA consumption should be encouraged as a replacement for saturated fatty acids (SFA), trans fatty acids, and (in some cases) refined carbohydrates.

Since the 1970s researchers have known that linoleic acid (LA) reduces blood cholesterol levels and lowers the risk of heart disease. Thus, it is no surprise that a recent American Heart Association (AHA) Science Advisory[2] recommended that omega-6 PUFA make up at least 5 to 10% of total energy. In addition, a current Position Statement from the American Dietetic Association (i.e., Academy of Nutrition and Dietetics) and Dietitians of Canada[3] noted that the recommended range of intakes for omega-6 PUFA

(primarily LA) in the U.S. from the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH)[4], the Institute of Medicine (IOM)[5] ranges from 5 to 10% of energy.


A linoleic acid (LA) molecule.

Despite the consistency of favorable recommendations regarding dietary LA, the possibility that this fatty acid contributes to excess inflammation has received considerable attention. The primary basis of concern is that large amounts of LA will prompt excessive formation of arachidonic acid (AA) and subsequent synthesis of pro-inflammatory eicosanoids (e.g., prostaglandin E_2 (PGE_2), leukotriene B_4 (LTB_4) and thromboxane A_4 (TXA_2).[6-10] Elevated pro-inflammatory eicosanoid generation could drive up other biomarkers of inflammation (e.g., interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP)) that are associated with increased incidence of cardiovascular disease (CVD), cancer and other chronic diseases. In addition, the possibility that high LA intake will result in decreased elongation of ALA to eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA) due to competition for the Δ-6 desaturase is a frequently stated concern.[8,11] This competition, in turn, could reduce the formation of anti-inflammatory eicosanoids, including the newly discovered resolvins and neuro-protectins that are derived from these longer-chain omega-3 fatty acids.[12] The literature in this field is very complex and numerous narrative reviews have been published that have come to different conclusions with respect to the possible pro-inflammatory effects of dietary LA.[13-17]

What the field was missing was a systematic review of randomized controlled trials that examined the impact of dietary LA on biological markers of inflammation among healthy adults. Therefore, in 2010 a colleague and I set out to fill this void in the literature. We conducted a search of the English and non-English literature using MEDLINE, the Cochrane Controlled Trials Register, and EMBASE to identify relevant articles. Fifteen clinical trials (seven cross-over and eight parallel studies) met the inclusion criteria (e.g., randomized, placebo-controlled intervention studies in healthy humans greater than one year of age in which the only fatty acid other than LA that was allowed to differ substantially between the experimental and control diets was oleic acid). The most frequently reported biomarker of systemic inflammation was circulating CRP. Surprisingly, there was no significant impact of varying LA intake on circulating CRP in any of these trials.[18] Furthermore, dietary LA showed no effect on circulating concentration of various other inflammatory biomarkers, including: IL-6, TNF-α, ICAM-1, L-selectin, P-selectin, fibrinogen, PAI-1, platelet activity (fibrinogen load), tPA/PAI-1 complex, TXB_2, PGE_2, $PGF_{2\alpha}$.[18]

In addition to these results from RCT (the gold standard in biomedical research), there have been a number of well-designed observational studies that have explored the relationship between LA intake and inflammation in humans. For example, Ferrucci and colleagues[19] observed that total omega-6 PUFA plasma concentrations were inversely associated with serum CRP, IL-6, IL-6r, IL-1ra, and TNF-α and paralleled the associations observed for total plasma omega-3 PUFA in a cross-sectional analysis of 1,123 Italian adults. In addition, Pischon and colleagues[20] observed that the lowest levels of inflammation were found in subjects who had the highest consumption of both omega-3 and omega-6 PUFA among 405 healthy men and 454 healthy women from the Health Professionals Follow-Up Study and the Nurses' Health Study, respectively. Other observational studies reported inverse and/or no association between plasma or dietary LA and a variety of markers of chronic inflammation.[21,22] The results from these and other epidemiological studies illustrate the weakness of "omega-6/omega-3 ratio" as a meaningful parameter. A more complete discussion of the shortcomings of the omega-6/omega-3 ratio has been published previously.[23]

There are several limitations in the data available for this first systematic review of the relationship between dietary LA and inflammation. First, all of the RCT incorporated small numbers of subjects. The largest study had only 60 subjects that completed the trial. Three of

the 15 RCT were conducted in metabolic wards, which enhanced the control over the dietary intervention, but had only six to nine subjects enrolled. A second limitation is the uncertain clinical relevance of various biomarkers of inflammation being measured in clinical studies. Often researchers measure multiple biomarkers of inflammation in the hope that one or more of them will have predictive value relevant to clinical outcomes. Many inflammatory biomarkers are characterized by considerable intra- and inter-individual variability. This variability makes it difficult to detect subtle changes with small sample sizes and the possibility of false negative outcomes cannot be dismissed. No consensus exists regarding which biomarker is best, since each has advantages and disadvantages, however, the linkage between CRP or fibrinogen and CVD risk is quite strong.[24] A third shortcoming of these RCT is their relatively short duration. The shortest trial was two weeks and the longest was 40 days. Two weeks is about the minimum amount of time required for diet-induced modifications of circulating and tissue fatty acids to stabilize.[25] However, the time required for dietary lipids to affect inflammation-related processes is less well understood.

Based on the current evidence from RCT and observational studies there appears to be virtually no data available to support the hypothesis that LA in the diet increases markers of inflammation among healthy, non-infant humans. However, in light of the limitations of the evidence available, one cannot fully reject the "diet LA drives inflammation hypothesis" at this time. To do so, will require additional data from larger and longer studies with meticulous dietary control that include subjects from differing genetic endowments. Nevertheless, the outcome of this recent systematic review should provide the dietetic and medical community with a measure of reassurance regarding current dietary recommendations that emphasize optimal intake of both omega-3 and omega-6 PUFA.

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Disclosure

KF is currently serving as a scientific advisor for the lipids committee of the International Life Sciences Institute of North America (ILSI-NA) MM