Linoleic Acid[1]

Linoleic acid (18:2ω6; cis, cis-9,12-octadecadienoic acid) is the most highly consumed PUFA found in the human diet. On consumption, linoleic acid has 4 primary fates. Like all fatty acids, it can be used as a source of energy. It can be esterified to form neutral and polar lipids such as phospholipids, triacylglycerols, and cholesterol esters. As part of membrane phospholipids, linoleic acid functions as a structural component to maintain a certain level of membrane fluidity of the transdermal water barrier of the epidermis. In addition, when released from membrane phospholipids, it can be enzymatically oxidized to a variety of derivatives involved in cell signaling [i.e., 13-hydroxy or 13-hydroperoxy octadecadienoic acid, 13-H(P)ODE].

As the parent compound for the family of ω6 PUFAs, linoleic acid can be elongated and desaturated to other bioactive ω6 PUFAs, such as γ-linolenic acid (18:3ω6) and arachidonic acid (20:4ω6). Subsequently, arachidonic acid can be converted to a myriad of bioactive compounds called eicosanoids, such as prostaglandins and leukotrienes. These eicosanoids are important in normal metabolic function of cells and tissues, but when persistently produced in excess, they are known to contribute to a number of chronic diseases, such as inflammation and cancer. It is this possible conversion to arachidonic acid for which linoleic acid has received the most notoriety. Although it has been hypothesized that limiting the intake of linoleic acid can reduce tissue levels of arachidonic acid, this does not seem to be the case in individuals who are consuming a typical Western diet. In tracer kinetic studies, fractional conversion of linoleic acid to arachidonic acid is believed to be between 0.3% and 0.6%, and this conversion appears to be offset by turnover.

After consumption and absorption by enterocytes lining the small intestines, linoleic acid is packaged into chylomicrons as phospholipids, triacylglycerols, or cholesterol esters and enters the general circulation (subclavian vein) via the thoracic duct. Linoleic acid is delivered to hepatic and extrahepatic tissues as chylomicrons are delipidated en route to and cleared by the liver during its transition to much smaller remnant particles. After cellular uptake, the fate of linoleic acid is determined by the needs of the tissue, i.e., incorporation into membrane phospholipids, desaturation and elongation, etc.

Deficiencies: Linoleic acid is an essential (indispensible) nutrient that contains 2 double bonds at the ninth and 12th carbons from the carbonyl functional group. Because humans cannot incorporate a double bond beyond the ninth carbon of a fatty acid, this fatty acid cannot be synthesized and thus must be consumed. As an essential component of ceramides, linoleic acid is involved in the maintenance of the transdermal water barrier of the epidermis. The level of essentiality in infants could be as low as 0.5–2.0% of energy and deprivation of linoleic acid (i.e., fat-free intravenous feeding) can result in scaly skin lesions, growth retardation, and altered plasma fatty acid patterns and thrombocytopenia (1). Because linoleic acid is abundantly found in infant formulas and foods and in human breast milk, essential fatty acid deficiency is extraordinarily uncommon in otherwise healthy individuals. Similarly, evidence of ω6 PUFA deficiency is extremely rare in the adult population in the absence of an inborn error of metabolism, i.e., a deficiency in FADS2 (fatty acid desaturase 2; Δ6 desaturase), a rate-limiting step in the desaturation of linoleic acid to arachidonic acid.

Diet recommendations: Typical intakes of linoleic acid in the United States diet are ~6% of energy. Although linoleic acid is an essential nutrient, "no specific information is available on the amount of linoleic acid required to correct the symptoms of (ω6) PUFA deficiency" (2); therefore, a recommended daily allowance (RDA) has yet to be established. As such, the dietary reference intakes for linoleic acid reports that the adequate intakes (AIs) for women and men between the ages of 19 and 50 y of age are 12 g/d and 17 g/d, respectively. The AI is based on approximate median intakes of healthy individuals in the US population. These amounts are modified to 11 g/d and 14 g/d for women and men, respectively, between the ages of 51 and 70 y of age. The Scientific Advisory Board of the American Heart Association recommends intakes between 5 and 10% of energy for adults to reduce the risk of coronary heart disease (3).

The AI for linoleic acid for children 1–3 y old (both sexes) is 7 g/d and progressively increases in boys and girls as they grow into adulthood. The AI for ω6 PUFAs (not just linoleic acid) in infants is based on the levels of ω6 PUFAs found in breast milk along with the transition to complementary foods. These levels are 4.4 g/d and 4.6 g/d for infants aged 0–6 mo and 7–12 mo, respectively (2).

Food sources: The major dietary sources of linoleic acid are vegetable oils, nuts, seeds, meats, and eggs. The consumption of linoleic acid in the US diet began to increase around 1969 and paralleled the introduction of soybean oil as the major commercial additive to many processed foods (4). Manufactured foods containing soybean oil as a primary ingredient will be rich in linoleic acid. Currently, soybean oil accounts for ~45% of dietary linoleic acid in the US diet. Nevertheless, linoleic acid is also the most abundant PUFA in most foods. Although linoleic acid accounts for ~88% of the total PUFAs in soybean oil, the levels in most commonly consumed foods exceed 70%. For example, of all the PUFAs in most meats

(beef, chicken, and pork), the contribution of linoleic acid is between 70 and 85% and >80% in eggs. Although it is well recognized that most vegetable oils are linoleic acid-based (noted exception is flaxseed), even foods with very low fat content (vegetables, fruits, and grains) are predominantly rich in linoleic acid as the major PUFA. Noted exceptions are beans, in which linoleic acid comprises between 40 and 50% of the total PUFAs.

Clinical uses: Because linoleic acid is an essential nutrient, it is typically provided in enteral, parenteral, and infant formulas where the fat content can vary depending on the specific use. Similarly, topical applications can also provide linoleic acid, helping to treat skin-related disorders related to deficiency. In the case of an inborn error in the metabolic step mediated by FADS2, more highly unsaturated fatty acids are provided to bypass this rate-limiting step.

Toxicity: No upper limit (UL) has been set for linoleic acid because of a lack of a defined intake establishing adverse affects (2). In epidemiologic studies, there is little evidence that suggests linoleic acid contributes to cardiovascular disease, cancer, or inflammation (where inverse correlations may exist). Nevertheless, consumption above recommended intakes should be carefully considered because there are equally insufficient data to adequately evaluate adverse effects at these higher levels.

Recent research: More than a century after linoleic acid was first described as an essential nutrient, there is a concern that current intake levels are unhealthy. It has been suggested that high dietary linoleic acid intake increases the incidence of chronic diseases, such as cardiovascular disease (CVD), cancer, and inflammation. The putative mechanism for these adverse health outcomes relates to the conversion of linoleic acid to arachidonic acid and the subsequent eicosanoids derived thereof. A couple of recent papers have undermined this theoretical model. For example, evidence suggests that modifying linoleic acid intakes has little effect on tissue arachidonic acid in humans (5). In 2009, the American Heart Association published an advisory that reviewed the data from randomized trials and case-control and cohort studies and came to the conclusion that at least 5–10% of energy from ω6 PUFAs (linoleic acid primarily) reduces the risk of CVD and that to reduce current levels would likely increase risk (3). The putative link between high linoleic acid intake and greater inflammation has been the subject of a recent systematic review. In this paper, the authors presented the findings from 15 randomized, controlled trials (8 parallel and 7 crossover designs) that permitted the effect of changing linoleic acid intake over a wide range to be assessed in healthy noninfant humans (6). Overall, the conclusion of this systematic review was that virtually no data exist supporting the hypothesis that dietary linoleic acid promotes inflammation in healthy humans. However, there is a concern that consuming high amounts of linoleic acid in the maternal diet has an impact on ω3 PUFA levels in the developing fetus (7), and high intakes could be associated with oxidative stress in early development (8). Despite the existence of a large body of research that supports current recommendations for linoleic acid intake, the controversy over whether there are adverse affects with high intakes of linoleic acid relative to ω3 PUFAs requires continued exploration.

More information about linoleic acid can be obtained from the Institute of Medicine's Dietary Reference Intakes (2,9).

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