



Dietary Linoleic Acid: Will Modifying Dietary Fat Quality Reduce the Risk of Type 2 Diabetes?

Matthias B. Schulze

Diabetes Care 2021;44:1903–1915 | <https://doi.org/10.2337/dci21-0031>

Linoleic acid (LA) is the major polyunsaturated fatty acid (PUFA) in Western diets; e.g., it accounts for almost 90% of PUFA intake in the U.S. diet (1). Intake levels as a percentage of total energy have increased over time in the U.S. (2), with mean intake being right within the range recommended by the U.S. Institute of Medicine (5–10%) (3). Although the intake of PUFA has been part of dietary recommendations for cardiovascular risk prevention, usually in the context of reducing intake of saturated fatty acids (SFA) (4), the American Diabetes Association does not clearly emphasize LA as a component of diet quality for diabetes prevention (5). This might be due to the fact that there are no available data from trials designed to investigate diabetes incidence as an outcome. However, prospective observational studies have now accumulated a substantial amount of data on the relation between LA intake or status and diabetes incidence, which helpful for reevaluation of its role for diabetes prevention.

In this issue of *Diabetes Care*, Mousavi et al. (6) summarize data from such prospective studies. They first systematically identified cohort studies on either dietary intake or tissue biomarkers of LA status and diabetes incidence. This led to nine cohorts on dietary intake, with a total of 22,639 cases of diabetes, and 27 cohorts on LA tissue biomarkers (including a total

of 18,458 incident cases). The authors then performed meta-analyses of individual study findings. With regard to dietary intake of LA, results of the meta-analysis suggest an inverse association. This was evident in considering different categories of intake and also from a dose-response analysis, where each additional 5% of energy from LA was associated with a 10% lower risk of type 2 diabetes. However, this observation seemed largely to be driven by the results of one individual cohort study, the Health Professionals Follow-up Study (HPFS) (7). In none of the other individual cohorts was a significant association observed, for several no indication for an inverse association was found at all, and leaving out the HPFS from analyses leads to attenuation and loss of significance (6).

Much clearer were associations for biomarkers of LA status. Individual cohort studies evaluated LA levels in different tissues and compartments, ranging from plasma cholesterol esters to plasma or erythrocyte phospholipids to adipose tissue. Nevertheless, inverse associations between higher LA content and diabetes risk were evident in many individual studies and in all meta-analyses, with the exception of adipose tissue, where only data from one individual cohort were identified (6). These associations were overall very robust against different sensitivity analyses; e.g., the association was

not driven by individual studies or dependent on the tissue used for biomarker determination. Overall, these findings are in line with previous reports from individual large-scale cohorts like EPIC-InterAct (8) or the cohort consortium FORCE (Fatty Acids and Outcomes Research Consortium) (9), which contributed a substantial proportion of data to the meta-analysis.

This leaves one with the question of whether the clear inverse association observed for LA biomarker levels can be used to support that higher dietary LA intake reduced diabetes risk—a conclusion not clearly supported by the cohort studies on dietary intake alone. For this, nutritional biomarkers would generally need to meet several qualifications. Importantly, they need to be sensitive to dietary intake. This has been found to be the case in several controlled feeding studies, although usually with doses above the recommended intake range (10). Moreover, a biomarker for LA intake should be specific for the intake of this PUFA and, thus, not affected by other factors. This can clearly be questioned given that lipid remodeling and PUFA metabolism have been shown to affect PUFA composition in various tissues (10). Importantly, LA is metabolized to longer-chain, more unsaturated PUFA, with the steps of desaturation (introduction of additional double bonds) being the rate limiting steps leading to the

Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany; German Center for Diabetes Research (DZD), Neuherberg, Germany; and Institute of Nutritional Science, University of Potsdam, Potsdam, Germany

Corresponding author: Matthias B. Schulze, mschulze@dife.de

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See accompanying article, p. 2173.

formation of arachidonic acid, a precursor for not only proinflammatory thromboxanes, 2 series prostaglandins, and the 4 series leukotrienes, but also for anti-inflammatory oxylipins (11). Thus, higher LA tissue concentrations may reflect higher dietary LA intake but also lower bioconversion to downstream PUFA and oxylipins.

That the cardiometabolic benefit of LA intake might depend on the degree of bioconversion has been indicated by genetic studies focusing on the *FADS1-2* gene cluster, which encodes the desaturases mentioned above (11). Interestingly, supplementation with LA-rich plant oils resulted in lower arachidonic acid phospholipid concentrations among those individuals with genetically lower ability for bioconversion (CC genotype of the *FADS1* variant rs174550), while arachidonic acid levels remained unchanged in individuals with normal desaturase activity (12,13). The *FADS1* variant also modified the response in β -cell function to LA, with a lower disposition index observed in those with lower bioconversion potential (13). However, studies evaluating the interplay between intake and metabolism of PUFA on cardiometabolic end points are quite limited. In the FORCE consortium of cohort studies, the inverse association of LA blood concentrations and diabetes did not depend on a higher or lower genetically determined ability to convert LA to AA and subsequent products (9). However, the *FADS* variant considered has already strong influence on LA tissue concentrations and interpretation of this PUFA biomarker as a proxy of dietary intake is, as discussed above, problematic. Clearly, prospective studies investigating associations between intake of dietary LA, instead of biomarkers, and subsequent risk of diabetes and its modification by variants in the *FADS1-2* gene cluster would be informative.

A further question is whether the observational finding of a reduced diabetes risk in this meta-analysis (6) reflects a causal association. Unfortunately, controlled trials provide limited evidence that modulating dietary LA affects important glycemic traits in individuals without diabetes (14); e.g., substitution of 5% energy from SFA by PUFA (thus mainly LA) does not significantly reduce fasting or 2-h glucose and insulin or HbA_{1c}. Trial results support, however, that such a substitution would lower insulin resistance measured by HOMA by

~4% (14). Thus, it is overall questionable whether a major shift in dietary fatty acid composition would translate to clinically relevant changes in important glycemic risk factors in individuals without diabetes. Noteworthy in this context, LA at the expense of SFA reduces LDL cholesterol levels (15); however, such a reduction would be expected to result in an increased risk of type 2 diabetes (16). To what extent the LDL-lowering effect of LA may counterbalance potentially beneficial effects of LA on diabetes risk remains unclear. Informative in this regard would be systematic investigations in cohort studies using specific macronutrient substitutions. Cohort studies included in the meta-analysis by Mousavi et al. (6) considered different adjustment models, with only three cohorts evaluating a substitution of LA for SFA (7). Similarly important, LA phospholipid levels have been found to correlate with other PUFA but also different SFA (e.g., inverse with palmitic acid) (17). Thus, low LA blood levels may also reflect a replacement by other fatty acids, e.g., SFA from de novo lipogenesis. As for cohort studies on LA intake, evaluating specific replacement patterns in consideration of LA biomarkers would be informative.

Given the inconsistent findings from cohorts on dietary LA intake and the problems of interpreting LA biomarker studies in terms of actual intake, conclusions from the meta-analysis regarding a role of higher LA in the diet as a measure to prevent diabetes may need to be made cautiously. On the other hand, this important meta-analysis clearly shows that harmful effects of increasing dietary LA should not be expected. This is important in that an increased intake of LA has been seen as problematic given its role as precursor for arachidonic acid and proinflammatory oxylipins (18,19). Moreover, dietary LA does have an important role in lowering cardiovascular risk irrespective of its potential role for diabetes prevention.

Funding. M.B.S. reports funding from the German Federal Ministry of Education and Research (BMBF) and the State of Brandenburg to the German Center for Diabetes Research (DZD036003) and from the European Commission and the German Federal Ministry of Education and Research (BMBF) in the Joint Programming Initiative a Healthy Diet for a Healthy Life, within ERA-HDHL

BioNH, the cofounded joint call for projects on “Biomarkers for Nutrition and Health” (01EA1704).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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