REVIEW

Increase in Adipose Tissue Linoleic Acid of US Adults in the Last Half Century[1,2]

Stephan J Guyenet[3] and Susan E Carlson[4]*

[3]independent researcher, Edmonds, WA; and [4]Department of Dietetics and Nutrition, University of Kansas Medical Center, Kansas City, KS

ABSTRACT

Linoleic acid (LA) is a bioactive fatty acid with diverse effects on human physiology and pathophysiology. LA is a major dietary fatty acid, and also one of the most abundant fatty acids in adipose tissue, where its concentration reflects dietary intake. Over the last half century in the United States, dietary LA intake has greatly increased as dietary fat sources have shifted toward polyunsaturated seed oils such as soybean oil. We have conducted a systematic literature review of studies reporting the concentration of LA in subcutaneous adipose tissue of US cohorts. Our results indicate that adipose tissue LA has increased by 136% over the last half century and that this increase is highly correlated with an increase in dietary LA intake over the same period of time. *Adv Nutr* 2015;6:660–4.

Keywords: subcutaneous adipose tissue, US, linoleic acid, dietary linoleic acid, change over time

Introduction

Linoleic acid (LA) (18:2n–6) is an 18-carbon n–6 PUFA with diverse effects on human physiology. LA is linked to skin barrier (1), immune (2), cardiovascular (3, 4), and neurobiological (5) functions, and, as a precursor of arachidonic acid and its metabolites, to reproductive (6), thermoregulatory, and digestive functions (7). In addition, LA is a natural ligand for PPARs (8). PPARs are intimately involved in the regulation of metabolic functions, including lipid and glucose metabolism, and they have been implicated in obesity and cardiometabolic disease risk (9). PPARα agonism may contribute to the ability of dietary LA to reduce circulating concentrations of total and LDL cholesterol (10). Finally, LA can influence biological processes via its nonenzymatic oxidation products. Oxidation of lipids in LDL is a risk marker for coronary heart disease (11). Because of its abundance in LDL and susceptibility to oxidation, LA is the most commonly oxidized species in LDL (12). The LA content of LDL reflects dietary intake (13).

Many seed oils are rich in LA, and consumption in the United States has increased substantially over the last half century (14). Much of this increase has come from soybean oil, which contains between 50% and 60% of total FAs as LA (14). Adipose tissue concentration of LA is particularly responsive to dietary LA, as demonstrated by diet modification trials (10). As such, it is used as a biomarker of dietary intake (15). We hypothesized that increases in dietary LA in the US food system have led to increased adipose tissue concentrations of LA. To test this hypothesis, we conducted a systematic literature review of studies that have reported the LA concentration of subcutaneous adipose tissue. Our findings suggest that adipose tissue LA has more than doubled in the United States over the last half century and correlates strongly with LA in the US food supply, potentially influencing numerous aspects of human physiology and pathophysiology.

Methods

To identify studies, a systematic search was conducted in May 2015 with the use of the PubMed and Google Scholar databases. Search terms included "adipose tissue fatty acids," "adipose tissue" and "fatty acids," and "adipose linoleic acid" and "adipose 18:2." Manuscripts were manually searched for additional references. All studies that reported adipose tissue LA concentration in US subjects before May 2015 were considered. Studies were excluded if subjects were infants, followed an atypical diet, or were diagnosed with a disease or had morbid obesity that could substantially influence FA concentrations in adipose tissue. We excluded nonsubcutaneous adipose depots because of potential differences in FA composition. In cases in which data from a study were reported in more than one publication, only results from the first report were included.

When provided in the manuscript, the date of adipose tissue sampling was used for analyses. When the date of sampling was not provided, the date of publication was used. Nineteen publications provided a sampling date, whereas 18 did not. More recent publications were more likely to provide a sampling date. In cases in which the date provided was a range, the mean value was used.

US LA intake data between 1909 and 1999 were estimated from USDA Economic Research Service food disappearance data, as previously described

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* To whom correspondence should be addressed. E-mail: scarlson@kumc.edu.

(14). A tabular version of the data was generously provided by Joseph R Hibbeln, MD (National Institute of Alcohol Abuse and Alcoholism). These data do not extend beyond 1999, and therefore the correlation analysis between LA intake and adipose tissue LA also does not extend beyond that date.

Statistics were performed in publicly available R software. Statistical significance was determined with the use of linear regression analysis.

Results

We identified 37 studies that met inclusion criteria, reporting 38 measurements of subcutaneous adipose tissue LA (**Table 1**). Publication dates ranged from 1959 to 2008, with no studies identified after this period. The most common sampling site was the buttocks (n = 20), although data also represent abdominal (n = 7), breast adipose (n = 4), posterior iliac crest (n = 2), calf (n = 1), perineum (n = 1), and unspecified subcutaneous adipose tissue (n = 3).

When considering all subcutaneous adipose sites, LA concentration increased in a linear manner over time (R^2 = 0.83; P < 0.001) (**Figure 1A**). The best-fit line for adipose tissue LA increased from 9.1% in 1959 to 21.5% in 2008, representing a 136% increase.

To eliminate possible confounding because of differences in adipose tissue composition across subcutaneous sites, we repeated the analysis including only data from the buttocks and abdominal tissue, which have a comparable FA composition (38). This had little impact on the strength of the relation between time and adipose tissue LA (R^2 = 0.86; P < 0.001) (Figure 1B).

Dietary LA has been shown to influence adipose tissue LA concentration in diet modification trials; however, to our knowledge, this hypothesis has never been evaluated by interrogating the correlation between LA intake and adipose tissue LA in a free-living population over a long period of time. Considering all subcutaneous sites, dietary intake of LA was highly correlated with adipose tissue LA (R^2 = 0.81; P < 0.001) (**Figure 2**). For every kg increase of yearly per capita LA intake, adipose tissue concentration of LA increased by 2%.

Conclusions

These findings support the hypothesis that adipose tissue LA concentration has greatly increased in the United States over the last half century. Between 1959 and 2008, adipose tissue

TABLE 1 Studies included in the analysis[1]

Publication	Date	% LA	Sample date	Site	Notes
Hirsch et al. (16)	1960	9.9	NS	Buttocks	
Gellhorn et al. (17)	1961	9.5	NS	Unspecified SC	
Scott et al. (18)	1962	9.5	NS	Abdominal SC	
Hegsted et al. (19)	1962	7.9	NS	Unspecified SC	
Dayton et al. (20)	1962	9	1959	Buttocks	Baseline
Lee et al. (21)	1962	12.1, 11.2	NS	Buttocks	US whites and blacks
Lee et al. (22)	1962	11.55	NS	Buttocks	Nondiabetics
Sweeney et al. (23)	1963	10.6	NS	Perineum SC	Mothers
Remenchik et al. (24)	1963	7.56	NS	Abdominal SC	
Christakis et al. (25)	1965	9.7	NS	Buttocks	Baseline
Rabinowitz et al. (26)	1965	8.7	NS	Abdominal SC	Baseline
Dayton et al. (10)	1966	11	1961 (estimated)	Buttocks	
Insull et al. (27)	1967	9.2	1962	Abdominal SC	
Fleischman et al. (28)	1968	11	NS	Buttocks	Baseline
Baker et al. (29)	1969	8.2	NS	Abdominal SC	Adults
Insull et al. (30)	1969	10.21	1966	Abdominal SC	
Insull et al. (31)	1970	10.2	1962, 1966	Abdominal SC	US whites and blacks
Witting et al. (32)	1975	13	1973	Buttocks	
Kokatnur et al. (33)	1979	11.5	1969–1971	Buttocks	
Fordyce et al. (34)	1983	13.68	NS	Posterior iliac crest	US-born Americans
Berry et al. (35)	1986	16.3	1981–1982	Buttocks	
Hill et al. (36)	1987	15.8	NS	Breast adipose	Controls
Handelman et al. (37)	1988	18.2	1986	Buttocks	
Malcom et al. (38)	1989	15.37	1986–1987	Buttocks	
Hudgins et al. (39)	1991	16.91	1981	Buttocks	
London et al. (40)	1991	17.23	1986–1987	Buttocks	
Hunter et al. (41)	1992	19	1986–1987	Buttocks	
London et al. (42)	1993	17.72	1986–1988	Buttocks	
Phinney et al. (43)	1994	18.72	NS	Unspecified SC	
Godley et al. (44)	1996	17.57	1989–1991	Buttocks	
Petrek et al. (45)	1997	16.59	1987–1989	Breast adipose	
Garland et al. (46)	1998	18.5	1986–1987	Buttocks	
Ullrich et al. (47)	2001	18	NS	Posterior iliac crest	Controls
Bagga et al. (48)	2002	13.9	1995–1996	Breast adipose	Controls
Knutsen et al. (49)	2003	20.1	NS	Buttocks	
Ren et al. (50)	2008	23.4	NS	Calf SC	
Yee et al. (51)	2010	18	2006–2008	Breast adipose	Baseline

[1] LA, linoleic acid; NS, not specified; SC, subcutaneous adipose tissue.

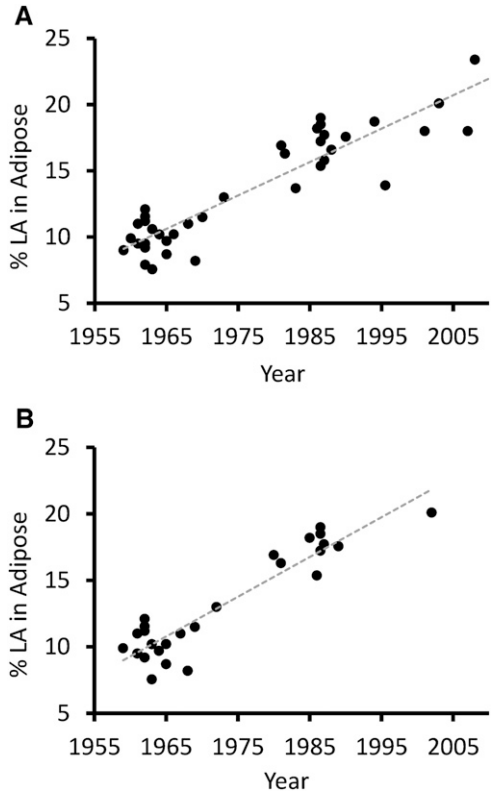

FIGURE 1 US adipose tissue LA concentration, 1959–2008. Increase in adipose tissue LA concentration over time across all subcutaneous sites ($R^2 = 0.83$; $P < 0.001$) (A). Increase in adipose tissue LA concentration over time, buttocks and abdominal subcutaneous only ($R^2 = 0.86$; $P < 0.001$) (B). LA, linoleic acid.

LA increased by 136%, representing a major shift in the adipose tissue concentration of a bioactive FA.

Because of its influence on multiple physiologic and pathophysiologic processes, LA has the potential to play an important role in human health. At the same time that the LA content of adipose tissue has been increasing, the United States has experienced substantial changes in disease prevalence. Cardiovascular disease risk has declined (52), whereas the prevalence of obesity (53), diabetes (54), and asthma (55) have increased. Our aim was not to evaluate the potential causal role of LA in these pathophysiologic processes, but simply to highlight that a role for LA in these trends is mechanistically possible and worthy of further investigation.

Our findings suggest that adipose tissue LA concentration is strongly correlated with dietary LA intake. This provides additional independent support for the hypothesis that long-term adipose tissue LA concentration is tied to dietary LA intake, and for the first time demonstrates that this relation applies to long-term population trends. Our analysis may also provide a basis for modeling the relation between population LA intake and adipose tissue LA. For each kg increase of estimated yearly per capita LA intake, adipose tissue LA increased by 2%. Because the half-life of LA incorporation into adipose tissue is ~680 d (10), changes in LA intake would take several years to result in a stable increase of adipose tissue LA.

Limitations of this study relate primarily to the nature of the underlying data. The data were not the result of longitudinal random sampling of the US population, but rather were primarily small samples representing varied regions of the United States. The underlying assumption is that local data, to some extent, represent broader population trends. However, local differences in dietary habits could reduce the applicability of individual data points to the United States as a whole. Furthermore, the results shown here are from laboratories that used different methods (e.g., packed compared with liquid-phase capillary columns or total adipose FAs compared with adipose tissue TG FAs) and reporting (e.g., weight percentage or area percentage). Some of the earlier studies may not have accounted for the longer chain (20- and 22-carbon) PUFAs, effectively increasing the proportion of LA in studies reported in the earlier years. Despite differences in methods that exist in the studies included in this cross-sectional study, we are unaware of any that would produce a large and systematic increase of LA. Our results are also limited by the fact that there are gaps in years of reported studies. In addition, 18 of 37 studies did not provide a sampling date, and therefore we used the publication date in analyses. In these cases, the sampling date occurred before the publication date, but the time difference is unknown. These limitations would all be expected to increase the variability of the data and decrease the likelihood of identifying statistically significant correlations. The fact that we were nevertheless able to identify strong positive relations between adipose tissue LA concentration and time ($R^2 = 0.81$–0.90; $P < 0.001$) argues that the data were of sufficient quality to address the hypotheses in question. Finally, estimates of LA intake used in Figure 2 are based on food disappearance data (14), which are not a direct measure of food intake. However, food disappearance estimates are likely more accurate than self-reported estimates, such as those from the CDC NHANES surveys, which are the primary alternative (56).

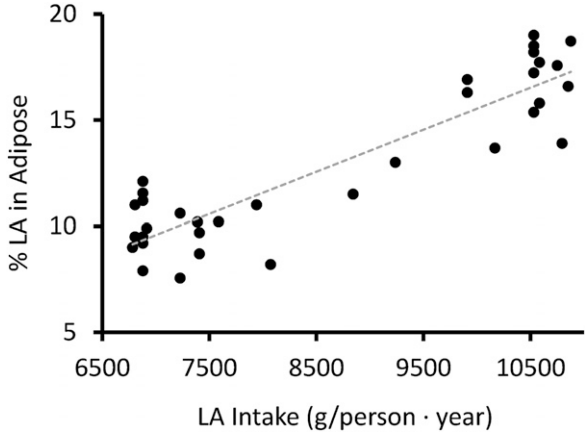

FIGURE 2 Correlation between adipose tissue LA concentration (all sites) and dietary LA intake, 1959–1999. Adipose tissue LA concentration is strongly correlated with dietary LA intake ($R^2 = 0.81$; $P < 0.001$). LA, linoleic acid.

Our findings suggest that adipose tissue LA has increased substantially in the United States over the last half century, and, to our knowledge, for the first time demonstrate that this increase is highly correlated with increased dietary LA intake over the same period. Interestingly, 3 recent investigations (2013–2015) of adipose tissue LA in European countries found concentrations of 11% (57), 12.5% (58), and 10.6% (59). These values are similar to earlier reports from the United States. Because LA is in involved in numerous physiologic and pathophysiologic processes, these changes have potentially significant implications for public health. These findings call for further research into the consequences, positive or negative, of such a major shift in the adipose tissue concentration of a single bioactive FA occurring over a relatively short period of time in the United States.

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