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Linoleic acid, glycemic control and Type 2 diabetes

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Abstract

Dietary fat quality, especially the intake of specific types of fatty acids, impacts the risk of many chronic diseases, including cardiovascular diseases, certain cancers and type 2 diabetes (T2DM). A recent pooled analysis involving 20 studies from around the world revealed that higher linoleic acid (18:2n-6 LA) biomarker is associated with dose-dependent decreases in the incidence of T2DM. This latest study corroborates earlier cross-sectional studies and intervention trials showing that biomarkers of LA intake are associated with reduced risk of T2DM and better glycemic control and/or insulin sensitivity. This review highlights key clinical trials that have evaluated the role of LA in glycemia and the related condition, insulin sensitivity.

Keywords

Adiponectin; Insulin resistance; Linoleic acid; Monounsaturated fat; Polyunsaturated fat; Saturated fat

1. Introduction

By 2050, an estimated 1/3 of US adults will have type 2 diabetes mellitus (T2DM) [1]. Unfortunately, co-morbidities of T2DM such as cardiovascular diseases, neuropathy, sleep apnea, blindness and depression, are all conditions that hasten mortality leading to 1 in 5 people dying as a result [1]. Pharmaceutical therapies for treating hyperglycemia in people with T2DM often have serious adverse side effects [2]. Lifestyle approaches offer alternative or complementary therapy to pharmaceutical treatment. Identifying dietary factors for managing hyperglycemia that are safe, effective, affordable and achievable is imperative to reduce the burden of T2DM on patients and the health care system.

Dietary fat quality (i.e., the fatty acid composition) is a component of the diet that may affect the management of hyperglycemia in people with T2DM. Fats comprise ~1/3 of calories in the typical US diet with saturated fatty acids (SFAs) comprising ~35%, monounsaturated fatty acids (MUFAs) ~40%, and polyunsaturated fatty acids (PUFAs) ~25% of fat energy. Higher intake of SFAs is generally related to increased risk of cardiometabolic diseases.

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In contrast, as early as 1994, studies have shown a consistent correlation between *higher* dietary or biomarker levels of the n-6 PUFA, linoleic acid (LA; 18:2n-6), and *lower* risk for T2DM [3–5]. A recent pooled analysis of 20 studies involving 39,740 people from 10 countries showed that higher levels of LA in blood were associated with a 43% lower relative risk for T2DM [3]. The dose-dependent decreases in T2DM were independent of age, BMI, sex, race, n-3 PUFA levels, aspirin use or Fatty Acid Desaturase (FADS) polymorphisms.

Indeed, it appears that a higher intake of PUFAs, especially of LA, is associated with improved glycemia. Over an average of a 5-year follow-up period, higher LA intake was associated with lower glycemia, measured by oral glucose tolerance tests, in nondiabetic men [6]. In addition, higher LA is associated with improved insulin sensitivity [7–9]. This review will summarize the literature evaluating LA biomarker status with glycemic control and highlight key clinical intervention studies evaluating the effect of LA-rich oils on glycemia and other T2DM-related conditions.

2. Clinical studies testing fat quality and glycemia

Numerous studies have attempted to identify the impact of SFAs, MUFAs and PUFAs on hyperglycemia in people with T2DM. In a landmark randomized controlled trial, the KANWU study sought to substitute MUFA-rich foods in place of SFA-rich foods in 162 healthy men and women [10]. The goal was to determine whether a change of fat source from SFAs to MUFAs could alter insulin sensitivity. After 12 weeks, the SFA-rich diet resulted in impaired insulin sensitivity and the MUFA-rich diet had no effect. These data underscore a role of many SFAs to worsen insulin sensitivity and a lack of a favorable effect of MUFA-rich diet on insulin sensitivity.

In attempts to evaluate a relationship of the MUFA, oleic acid (18:1n-9), in disease risk, some investigators have attempted to link the Mediterranean diet with decreased risk for cardiometabolic diseases. The Mediterranean diet is a dietary pattern characterized by higher intake of fruits, vegetables, legumes, fish, whole grains, nuts, and olive oil, a rich source of the MUFA, oleic acid. Indeed, this dietary pattern was associated with lower risk for cardiac disease and T2DM [11]. Yet, most studies fail to recognize that olive oil is not the sole dietary source of fatty acids in the Mediterranean diet; it is but one of many fatty acid sources in this dietary pattern. In fact, neither blood oleic acid levels nor the intake of MUFAs were associated with a change in T2DM risk in the Cardiovascular Health Study [12]. Further, in the PREDIMED study, there was no association of plasma oleic acid with reduced incidence of the metabolic syndrome [13]. The findings of the KANWU intervention study mirror findings from epidemiological and cross-sectional studies suggesting a *lack of SFAs* may be most impactful for modulating insulin resistance; whereas, adding MUFAs may have only a marginal, if any, effect. To our knowledge, a side-by-side trial comparing the effects of supplementing with MUFA-rich oil vs. SFA-rich oil on glycemia or insulin sensitivity in people with T2DM has not been conducted.

A meta-analysis of studies evaluating fish oil-derived long chain n-3 PUFAs, e.g., eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), and

glycemic control have found weak to no relationship between the two [14]. Interestingly, an effect of supplementation of EPA/DHA-rich oils may be relevant in people with metabolic syndrome but not relevant in non-obese, normo-glycemic people [14]. In particular, randomized controlled trials testing EPA/DHA oils on insulin sensitivity failed to show an effect of n-3 PUFAs on glucose disposal when measured using the euglycemic-hyperinsulinemic clamp [15,16]. Because some trials show that supplementation with EPA/DHA oils reduce inflammation [17], the usage of n-3 PUFAs to improve co-morbidities of T2DM, other than insulin resistance, might still be useful for people with T2DM.

Although there are inconsistent or null effects of MUFA and n-3 PUFA interventions on insulin resistance or glycemic control, several studies show *higher* LA levels in the diet or blood are associated with better insulin sensitivity [4,7,18,19]. There have been a handful of randomized controlled trials testing the impact of LA-rich oils on insulin sensitivity or glycemic markers (summarized in Table 1). In a seminal study, adults were assigned to one of two diets in a crossover intervention to test LA-rich or SFA-rich foods [20] on insulin sensitivity as measured by a hyperinsulinemic-euglycemic clamp. Each diet period lasted five weeks. Compared to insulin sensitivity after the SFA diet period, insulin sensitivity was significantly better after five weeks consuming the LA-rich diet. Because LA-rich oil was substituted for SFAs, it was not possible to confirm that the effects of the LA-rich diet was attributed to LA or the lack of SFAs. In this study, women showed a reduction of visceral adipose mass measured by magnetic resonance imaging with the LA-rich oil; an effect of the LA-oil on visceral adipose mass in men was not evident [21].

In a more recent study, we conducted a randomized controlled crossover trial where women with T2DM were supplemented with either LA-oil or conjugated linoleic acid (CLA)-oil capsules for 16-week diet periods separated by a 4-week wash-out period [22,23]. LA-oil supplementation resulted in significant improvements of glycemic control (e.g., fasting glucose and HbA1c, high-density lipoprotein and C-reactive protein). Furthermore, when women were supplemented with LA-oil, lean mass increased and trunk adipose mass was reduced as measured by dual x-ray absorptiometry. In our study, the effects of LA-oil were different than CLA-oil which had no impact on glycemia, high density lipoprotein, C-reactive protein, trunk adipose or lean mass [23]. Intriguingly, LA-oil supplementation increased plasma adiponectin, an adipokine often associated with increased insulin sensitivity through peripheral effects on metabolism in muscle and liver.

In two newer interventions using food-based delivery of LA-oil, participants were provided instruction and foods containing LA-rich oils vs. SFA-rich fats to influence: 1) hepatic steatosis in overweight adults [24]; or 2) weight gain patterns in non-obese adults [25]. Compared to SFA-rich foods, LA-rich foods reduced hepatic steatosis and markers of inflammation [24]. When provided as additional calories that lead to weight gain, LA-rich foods increased lean mass accretion by almost 3-fold more than changes of lean mass in people fed SFA-rich fats [25]. These findings corroborate observational studies in cohorts where higher LA status (measured in diet, blood or adipose tissue) was associated with lower risk of T2DM [3–5,26], better insulin sensitivity [4,7,18,19], reduced trunk or visceral adipose mass [24,25,27], increased lean mass [19,24,25,28,29] and reduced markers of inflammation [19,30,31].

Because of the intriguing effects of LA-oils on insulin sensitivity [21] and body composition [19,24,25,27], we recently completed a pilot study to determine the impact of LA-oil on plasma adiponectin and high molecular weight (HMW) adiponectin profiles [32]. HMW adiponectin is the bioactive form that stimulates mitochondria capacity in liver and skeletal muscles [33]. Post-menopausal women with metabolic syndrome were enrolled into an open label, single-arm 16-week intervention. Participants were instructed to consume 9.3 g/d LA-rich oil by adding to foods such as yogurt, breakfast oatmeal and salad dressings. Biomarker levels of LA in erythrocytes were variable between participants suggesting that compliance was also variable. However, plasma adiponectin and HMW-adiponectin increased and erythrocyte LA was associated with improved insulin sensitivity.

In a recent epidemiological study, plasma LA was associated with decreased intramyocellular lipid levels in older adults [34]. Interestingly, erythrocyte LA status declines approximately 10% per decade between the ages of 50 and 80 years [35]. The decline of LA status could contribute directly to the loss of insulin sensitivity that accompanies aging. To our knowledge this has not been tested.

The association of higher LA status with reduced risk for heart diseases [36–38] and T2DM [3–5], as well as a role of LA-oils to improve insulin sensitivity and modulate body composition, argue for a key role of LA-rich oils to promote cardiometabolic health. Future studies are needed to identify optimal levels of dietary LA to reduce chronic diseases and deaths associated with insulin resistance and associated conditions.

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Table 1

Summary of Intervention trials testing effects of LA-oils on glycemic control.

Title/Citation	Cohort	Design/Dose/ Delivery of LA	End points	Findings
Summers et al. (2002) [20]	N = 17	Cross-over design to study effect of SFAs vs. LA on insulin sensitivity	Fatty acid composition, plasma	Plasma LA increased 10% after LA diet period
	Men & women (Non-obese, N = 6; Obese, N = 5; T2DM, N = 6)	5-week diet periods of SFAs or LA delivered through foods Non-random order of fats	Insulin sensitivity, clamp Visceral adipose, MRI	LA increased insulin sensitivity and decreased visceral adipose
		Goal: To add ~ 5 g LA/d to achieve ~ 20 g LA/d (total)		
Norris et al. (2009) [23]	N = 55	Cross-over design to study effect of LA vs. CLA on glycemia and body composition	Fatty acid composition, plasma	Plasma LA increased 10% after LA diet period
Aspetal. (2011) [22]	Obese, postmenopausal women with T2DM	16-week diet periods with 4-week wash-out period	Insulin resistance, HOMA-IR	LA treatment decreased insulin resistance and trunk adipose and increased lean mass and adiponectin; CLA had no effect on these outcomes
		LA or CLA delivered through capsule supplements	Body composition, DEXA Adipokines	
	Oral hypoglycemic medications	Goal: To add ~6g LA/d to achieve ~ 18g LA/d (total)		
Bjermo et al. (2012) [24]	N = 67 centrally obese men and women with/ without T2DM	10-week parallel arm to study liver steatosis	Fatty acid composition, serum	Serum LA increased 11% after LA diet period
		SFAs vs. LA delivered through foods	Insulin resistance HOMA-IR	LA group had decreased liver fat with no change of insulin resistance (vs. SFA)
		Goal: To achieve ~ 21 g LA/d (total)	Liver fat, MRI	
Rosqvist et al. (2014) [25]	N = 39	7-week parallel arm to study liver fat change after weight gain	Fatty acid composition, plasma	Serum CE LA increased ~ 12% in LA-oil group
Iggman et al. (2014) [39]	Non-obese men & women	Over-feed participants (+ 3%)	Body composition for liver fat, visceral adipose and muscle, MRI	LA decreased hepatic steatosis and increased lean mass gain (vs. SFAs)
		SFAs vs. LA delivered through foods Goal: To Achieve ~17g LA/d (total)		
Cole et al. (2016) [32]	N = 15 women with MetS	16-week single-arm, non-blind to explore changes of oxylipin profile (not intent-to-treat) in relation to adiponectin Goal: To add ~ 7 g LA/d to achieve ~ 18 g LA/d (total)	Fatty acid composition, erythrocytes	Erythrocyte LA, no change
			Oxylipin lipidomic analysis Adiponectin	LA increased, adiponectin, HMW adiponectin LA biomarker was associated with increased lean mass

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