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Influence of Dietary Saturated Fat Intake on Endothelial Fibrinolytic Capacity in Adults

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Abstract

Approximately 50% of middle-aged and older adults in United States regularly consume a diet high in saturated fat. High dietary saturated fat intake has been linked to promoting atherothrombtic vascular disease. We tested the hypothesis that endothelial fibrinolytic function is diminished in middle-aged and older adults who habitually consume a diet high in saturated fat. Twenty-four healthy, sedentary middle-aged and older adults (54–71 years) were studied: 10 (8 males/2 females) with a dietary saturated fat intake <10% (lower saturated fat) of total calories; and 14 (9 males/5 females) with a dietary saturated fat intake ≥10% of total calories (high saturated fat). Net endothelial release of tissue-type plasminogen activator (t-PA), the primary activator of fibrinolysis, was determined, *in vivo*, in response to intrabrachial infusions of bradykinin (12.5–50.0 ng/100 mL tissue/min) and sodium nitroprusside (1.0–4.0 μg/100 mL tissue/min). Capacity of the endothelium to release t-PA in response to bradykinin was <30% less ($P<0.05$) in the high (from −0.7±0.6 to 36.9±3.3 ng/100 mL tissue/min) compared with lower (from −0.3±0.3 to 53.4±7.8 ng/100 mL tissue/min) dietary saturated fat group. Moreover, total amount of t-PA released was significantly less (~30%) (201±22 vs 274±29 ng/100 mL tissue) in the adults who reported consuming a diet high in saturated fat. These results indicate that the capacity of the endothelium to release t-PA is lower in middle-aged and older adults who habitually consume a diet high in saturated fat. In conclusion, endothelial fibrinolytic dysfunction may underlie the increased atherothrombotic disease risk with a diet high in saturated fat.

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Keywords

diet; saturated fat; fibrinolysis; tissue-type plasminogen activator

INTRODUCTION

Middle-aged and older adults are at heightened risk for cardiovascular disease (CVD) due, in part, to impaired vascular endothelial function.[1,2] The endothelium plays a central role in the regulation of vasomotor tone and fibrinolytic function.[3] Endogenous fibrinolysis is the primary defense mechanism against thrombosis,[4] and endothelial cells are the principal site of synthesis and release of tissue-type plasminogen activator (t-PA), the main activator of the fibrinolytic system.[5] We have previously shown that endothelial release of t-PA declines with advancing age[6] and likely contributes to the increased risk of atherothrombotic events in middle-aged and older adults.[7] The influence of dietary saturated fat intake on endothelial fibrinolytic function is not well understood. There are some data to suggest that dietary fat adversely influences plasma fibrinolytic concentrations;[8,9] however, it is the capacity of the endothelium to acutely release t-PA and not circulating plasma fibrinolytic concentrations that determines the efficacy of endogenous fibrinolysis.[4,10] Moreover, circulating plasma fibrinolytic proteins provide an indirect, nonspecific and potentially misleading assessment of fibrinolytic potential.[10] The aim of the present study was to determine the influence of dietary saturated fat intake on endothelial fibrinolytic function in middle-aged and older adults. We hypothesized that the capacity of the endothelium to release t-PA would be diminished in middle-aged and older adults who habitually consume a diet high in saturated fat. To address this aim, we used an isolated forearm model to assess, *in vivo*, endothelial t-PA release in middle-aged and older adults with differing dietary habits.

METHODS

Twenty-four healthy, sedentary middle-aged and older adults age 54–71 years (17 males/ 7 females) were studied (Table 1): 10 (8 males/ 2 females) with a dietary saturated fat intake <10% (lower saturated fat) of total calories; and 14 (9 males/5 females) with a dietary saturated fat intake ≥10% of total calories (high saturated fat). Dietary saturated fat intake classifications were based on Dietary Guidelines for Americans that recommend consuming less than 10% of total calories from saturated fat.[11]

Subjects were excluded from the study if they presented a history or evidence of: hepatic, renal, or hematological disease; peripheral vascular disease; stroke; diabetes (fasting plasma glucose > 125 mg/dL); dyslipoproteinemia (total cholesterol ≥ 240 mg/dL, triglycerides ≥ 300 mg/dL); and hypertension (arterial blood pressure ≥ 140/90 mmHg). All subjects were screened for clinical evidence of cardiovascular disease by medical history, physical examination, fasting blood chemistries, and electrocardiograms and blood pressure at rest and during incremental exercise performed to exhaustion. None of the subjects smoked or were taking medications including vitamins. All of the women were at least 1 year postmenopausal and had never taken or had discontinued use of hormone replacement therapy at least 1 year before the start of the study. Prior to participation, all of the subjects

had the research study and its potential risks and benefits explained fully before providing written informed consent according to the guidelines of the University of Colorado at Boulder.

Body mass was measured to the nearest 0.1 kg using a medical beam balance (Detecto, Webb City, MO). Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Percent body fat was determined by dual energy X-ray absorptiometry (Lunar Corp., Madison, WI). Minimal waist circumference was measured according to published guidelines.[12] To assess aerobic fitness, subjects performed incremental treadmill exercise with a modified Balke protocol, as previously described.[1] Maximal oxygen consumption ($\dot{V}O_2$ max) was measured with on-line computer-assisted open circuit spirometry.

Fasting plasma lipid, lipoprotein, glucose, and insulin concentrations were determined using standard techniques as previously described.[13] Plasma concentrations of the inflammatory cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-18, and C-reactive protein (CRP) as well as oxidized low-density lipoprotein (ox-LDL), a marker of oxidative stress, were determined by enzyme immunoassay (R&D Systems, Minneapolis MN and ALPCO Diagnostics, Windham, NH).

Subjects were instructed by a bionutritionist at the University of Colorado, Boulder Clinical and Translational Research Center (CTRC) on how to record their dietary intake for 4 days (3 consecutive weekdays and 1 weekend day) and to not alter their regular diet during the study period. All completed dietary recall records were analyzed by the CTRC bionutritionist using the Food Processer nutrition software (ESHA Research, Salem, OR).

All measurements were performed in a temperature-controlled room between 7 and 10 AM after a 12-hour overnight fast as previously described by our laboratory.[13] Briefly, an intravenous catheter was placed in a deep antecubital vein of the nondominant arm. Thereafter, a 5-cm, 20-gauge catheter was introduced into the brachial artery of the same arm under local anesthesia (1% lidocaine). Forearm blood flow (FBF) was measured using strain-gauge venous occlusion plethysmography (D.E. Hokanson, Bellevue, WA) and presented as mL/100 mL forearm volume/min. Following the measurement of resting blood flow for 5 minutes, bradykinin was infused intra-arterially at rates of 12.5, 25.0, 50.0 ng/100 mL tissue/min and sodium nitroprusside at 1.0, 2.0, 4.0 μg/100 mL tissue/min for 5 min at each dose as previously described.[14] To avoid an order effect the sequence of drug administration was randomized. Forearm volume was determined by the water displacement method. Net endothelial release of t-PA and plasminogen activator inhibitor-1 (PAI-1) antigen in response to bradykinin and sodium nitroprusside was calculated according to Jern et al.[15] using the following equation:

$$\text{Net Release} = (C_V - C_A) \times [(\text{FBF} \times (101 - \text{hematocrit}/100)]$$

where C_V and C_A represent the concentration in the vein and artery, respectively. Arterial and venous blood samples were collected simultaneously at baseline and at the end of each drug dose. t-PA and PAI-1 antigen concentrations were determined by enzyme

immunoassay in each blood sample. Hematocrit was measured in triplicate using the standard microhematocrit technique and corrected for trapped plasma volume within the trapped erythrocytes.[16] The total amount of t-PA antigen released across the forearm in response to bradykinin was calculated as the total area under each curve above baseline using a trapezoidal model. To avoid confounding effects from potential infection/inflammation-associated fibrinolytic changes, all subjects were free of recent infection/inflammation (<2 wk), as determined by questionnaire.[17]

Differences in subject baseline characteristics and area under the curve data between groups were determined by analysis of variance (ANOVA). Group differences in FBF and endothelial t-PA and PAI-1 antigen release in response to bradykinin and sodium nitroprusside were determined by repeated-measures ANOVA. When indicated by a significant F value, a post hoc test using the Newman-Keuls method was performed to identify differences between the groups. Relations between variables of interest were assessed by means of Pearson's correlation coefficient and linear regression analysis. There were no significant gender interactions in any of the primary outcome variables; therefore, the data were pooled and presented together. All data are expressed as means ± SEM. Statistical significance was set a priori at $P < 0.05$.

RESULTS

Selected subject characteristics are presented in the table. Aside from percent body fat, there were no differences between the groups in any anthropometric, hemodynamic, physical fitness, or metabolic variables. There were no significant differences between the groups in total caloric intake or percent of calories from carbohydrates and protein. By design, percent of calories from fat was significantly different between the groups. Saturated fat intake, in particular, was ~80% greater in the high dietary saturated fat group than the lower dietary saturated fat group. There were no significant differences in plasma concentrations of TNF-α(2.0±0.2 vs 2.8±0.9 pg/mL), IL-6 (2.6±0.5 vs 2.7±0.8 pg/mL), C-reactive protein (2.7±0.8 vs 1.7±0.7 mg/L) and oxLDL (60±4 vs 57±7 U/L) between the high and lower saturated fat groups. Plasma concentrations of IL-18 were ~40% ($P<0.05$) higher in the high (261±19 pg/mL) compared with lower (177±20 pg/mL) dietary saturated fat group.

FBF responses to bradykinin and sodium nitroprusside were not significantly different between the groups (Figure 1). Figure 2 shows net endothelial t-PA release and total t-PA release (area under the bradykinin curve) in response to bradykinin in the groups. Although there were no group differences in basal endothelial t-PA release, net release of t-PA antigen in response to bradykinin was approximately 30% less ($P<0.05$) in the high (from −0.7±0.6 to 36.9±3.3 ng/100 mL tissue/min) compared with lower (from −0.3±0.3 to 53.4±7.8 ng/100 mL tissue/min) dietary saturated fat group. Consequently, the total amount of t-PA released in response to bradykinin was significantly less (~30%) (201±22 vs 274±29 ng/100 mL tissue) in the adults who reported consuming a diet high in saturated fat. Net release of t-PA antigen in response to sodium nitroprusside was not significantly different between the groups (Figure 2). Neither bradykinin nor sodium nitroprusside elicited a change in PAI-1 antigen release in either group (data not shown). Although percent body fat was significantly different between the groups, percent body fat was not significantly correlated with either

basal or bradykinin-stimulated t-PA release in either group or the total study population (data not shown).

DISCUSSION

The novel finding of the present study is that dietary saturated fat intake is associated with blunted endothelial t-PA release in middle-aged and older adults. Indeed, the capacity of the endothelium to release t-PA was ~30% lower in adults whose habitual diet was characterized by high saturated fat intake (>10% of total calories from saturated fat). To our knowledge, this is the first study to determine whether habitual saturated fat intake influences endothelial fibrinolytic function. Blunted endothelial t-PA release may contribute to the increased atherothrombotic risk associated with high saturated fat diets.

The relation between dietary fat intake and cardiovascular disease morbidity and mortality has been extensively studied.[18,19] For example, data from the Nurse's Health Study involving 14 years of dietary reporting indicated that saturated fat intake is strongly and positively correlated with CHD risk.[18] Further, a Cochrane Review of studies comprising over 65,000 adults found that reducing saturated fat intake significantly decreases the risk of cardiovascular events.[20] As a result, public health recommendations emphasize the importance of limiting saturated fat intake as a feasible means to reduce the risk of atherosclerotic disease.[21] Traditionally, the classic diet-heart hypothesis has attributed the role of saturated fat in cardiovascular disease pathology to elevated levels of LDL-cholesterol.[19] The results of the present study significantly extend this hypothesis by demonstrating a link between dietary saturated fat intake and diminished endothelial release of t-PA. The ability of the endothelium to acutely and locally release t-PA is essential to maintaining vascular health. Endothelial t-PA release protects against aberrant fibrin formation and thrombogenesis, ultimately reducing the risk of atherothrombotic events. [4,22] In the present study, the capacity of the endothelium to release t-PA was markedly lower in middle-aged and older adults who regularly consumed a diet high in saturated fat. Of note, the negative influence of high dietary saturated fat intake was observed in middle-aged and older adults, a population known to already have deficient endothelial t-PA.[6] Thus, a diet high in saturated fat appears to worsen the capacity of the endothelium to release t-PA in middle-aged and older adults, further increasing the atherothrombotic potential in an already at risk population. From a clinical perspective, it is estimated that >50% of middle-aged and older adults in the United States regularly consume a diet with a saturated fat content of >10% of total calories.[23] The potential negative vascular consequences of a diet high in saturated fat heightens the need for continued clinical surveillance of dietary habits in middle-aged and older adults.

The exact mechanisms by which high dietary saturated fat intake may adversely influence t-PA release are not clear, though increased oxidative stress and inflammation may be important mediators. High saturated fat intake induces a pro-oxidative state[24] and increased oxidative stress has been shown to adversely affect the capacity of the endothelium to release t-PA.[25] Although oxLDL concentrations were not different between the two groups in the present study, this does not discount the possibility of an oxidative stress mediated mechanism. Circulating markers of oxidative stress provide poor representation of the focal

oxidative environment at the level of the vessel wall. With respect to inflammation, we have previously shown that t-PA release is inversely related to plasma concentrations of C-reactive protein.[26] Schwartz et al.[27] have demonstrated that saturated fatty acids promote a pro-inflammatory environment via binding to toll like receceptor-4 (TLR-4) on macrophages, thus activating the NFκB pathway and subsequent transcription of pro-inflammatory cytokines. Of note, in the present study IL-18 concentrations were higher in individuals who regularly consumed a diet high in saturated fat compared with lower saturated fat consumption. *In vitro* work supports this finding as palmitic acid, a saturated fatty acid, has been shown to elevate IL-18 concentrations.[28] Future studies are needed to delineate the underlying mechanisms of the apparent deleterious effect of habitual high dietary saturated fat intake on endothelial t-PA release.

There are a number of experimental considerations regarding the present study that deserve mention. First, self-report of diet is inherently subject to bias; however, food diaries are most closely associated with actual intake than any other dietary measure (i.e. 24 hour recall, food frequency questionnaires) in free-living humans.[29] Moreover, at least three days of food diaries are considered necessary to adequately estimate energy intake;[30] in the present study we utilized four-day food diaries in order to assess both week day and weekend intake. Further, the diet record approach has been validated against weighed food records collected over a one-year period.[29] Secondly, given the fundamental limitations with a cross-sectional study design, we cannot completely dismiss the possible influence of genetic and/or lifestyle factors on our findings. To limit lifestyle factors we studied sedentary, non-smoking, adults who were not taking medications or vitamin supplements that could influence endothelial fibrinolytic function. In addition, we employed strict inclusion criteria to eliminate the confounding effects of clinically overt cardiovascular and metabolic disorders that are prevalent in middle and older age. However, all subjects in this cohort were non-Hispanic white adults, which limits our ability to extend these results to other racial/ethnic groups. Lastly, the results of the present study should be viewed within the context of our subject demographics; whether diets high in saturated fats have a similar detrimental influence on endothelial t-PA release in young healthy adults or adults with known disease is unknown.

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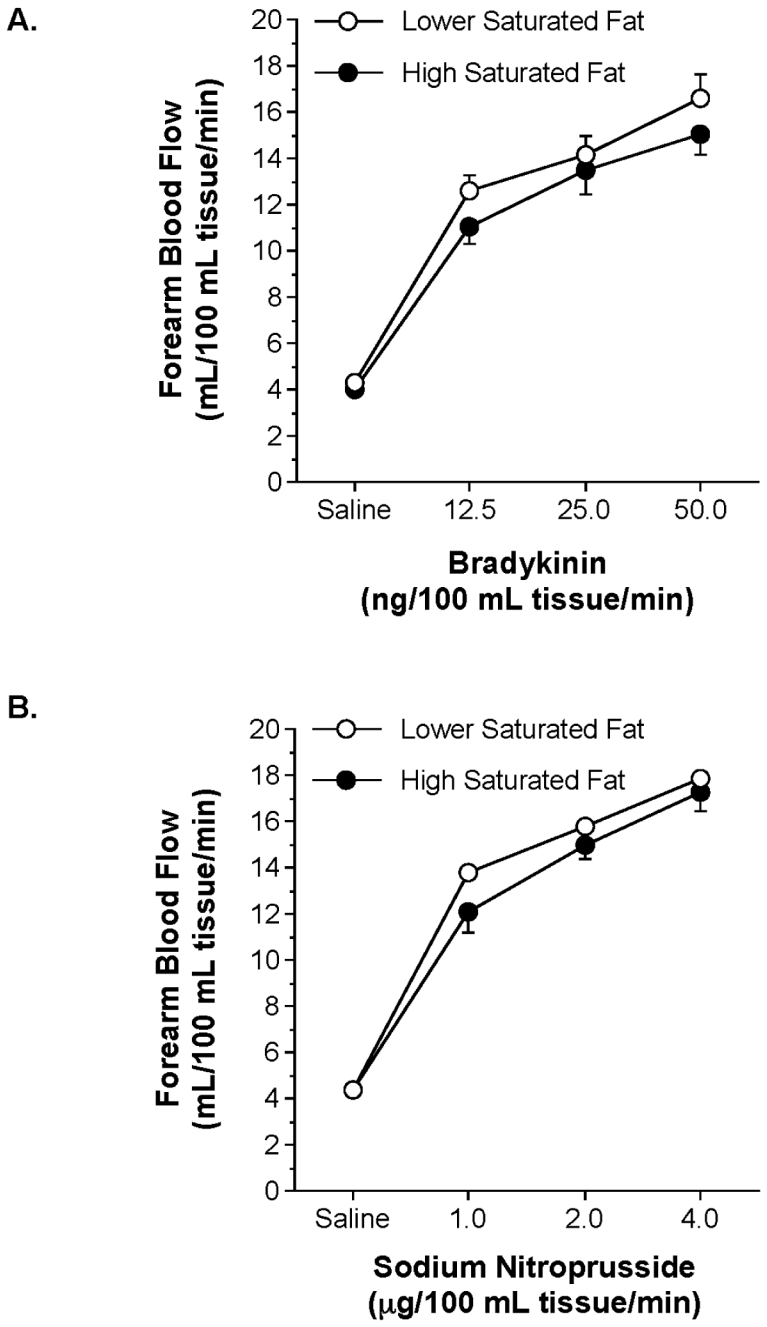

Figure 1.

Forearm blood flow (FBF) responses to bradykinin (Panel A) and sodium nitroprusside (Panel B) in adults who habitually consume a diet lower and high in saturated fat. Values are means ± SEM.

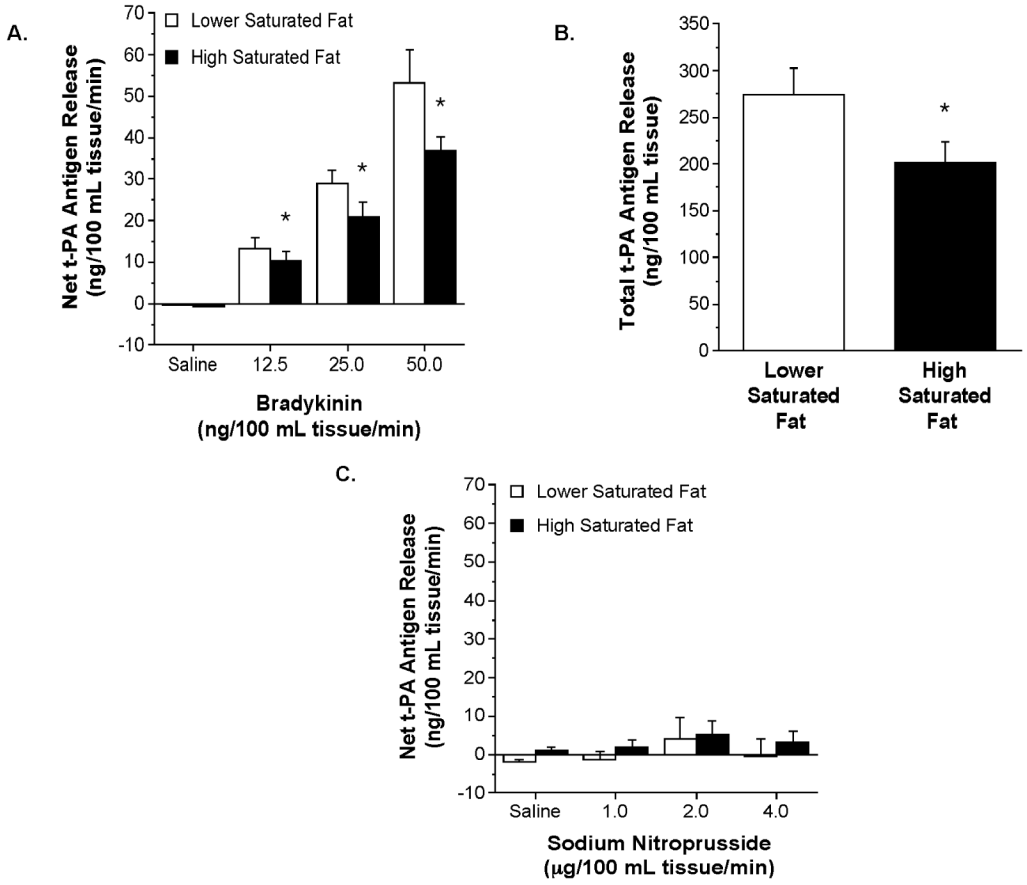

Figure 2.

Net release rate (Panel A), total amount (Panel B) of tissue-type plasminogen activator (t-PA) antigen released (area under the curve) in response to bradykinin and t-PA net release rate to sodium nitroprusside (Panel C) across the forearm in adults who habitually consume a diet lower and high in saturated fat. Values are means ± SEM; *P<0.05 vs. lower saturated fat.

Table 1

Selected subject characteristics

	Body mass (kg)	BMI (kg/m^2)	VO_2 max (mL/kg/min)	Total Calories (kcal)	Carbohydrates (%)	Protein (%)	Fat (%)	Saturated fat (%)
Lower Saturated Fat Subject Age (yrs)								
54	67.0	23.5	31.3	2887	46	16	38	9
56	90.4	30.2	32.4	3137	52	14	34	9
57	73.1	23.9	42.0	2872	46	19	21	6
58	93.7	28.3	31.6	2331	45	15	30	6
58	99.6	30.4	35.4	1625	47	19	34	6
59	83.0	26.8	30.5	3913	37	22	40	8
63	56.6	20.8	24.9	1778	46	21	34	8
64	92.5	29.2	28.4	1653	45	15	30	6
67	82.0	25.9	24.5	2009	43	14	25	7
71	91.2	29.8	21.0	2319	48	15	37	8
High Saturated Fat Subject Age (yrs)								
54	96.5	30.5	30.5	1972	45	18	37	14
54	79.1	28.7	20.1	2091	35	14	49	19
57	97.4	31.1	26.0	1961	35	11	54	13
58	90.8	28.7	28.3	2376	39	12	50	13
58	93.9	33.3	26.4	1164	49	20	31	10
58	87.7	31.5	18.1	2365	46	15	36	13
58	96.2	39.5	17.1	1542	54	15	32	12
59	84.9	26.8	35.0	2193	30	20	41	18
61	73.0	22.0	29.3	2547	58	11	31	10
62	88.0	29.1	31.4	1783	42	19	29	10
62	81.7	27.9	34.1	2648	28	18	50	14
65	93.0	28.7	24.5	2933	44	14	39	10
69	75.1	29.7	20.9	2034	56	12	32	11
70	81.0	27.4	27.4	2799	55	12	32	16