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Influence of habitual high dietary fat intake on endothelium-dependent vasodilation

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Abstract

High-fat diets are associated with an increased risk of cardiovascular disease. A potential underlying mechanism for the increased cardiovascular risk is endothelial dysfunction. Nitric oxide (NO)-mediated endothelium-dependent vasodilation is critical in the regulation of vascular tone and overall vascular health. The aim of this study was to determine the influence of dietary fat intake on endothelium-dependent vasodilation. Forty-four middle-aged and older sedentary, healthy adults were studied: 24 consumed a lower fat diet (LFD; $29\% \pm 1\%$ calories from fat) and 20 consumed a high-fat diet (HFD; $41\% \pm 1\%$ calories from fat). Four-day diet records were used to assess fat intake, and classifications were based on American Heart Association guidelines ($<35\%$ of total calories from fat). Forearm blood flow (FBF) responses to acetylcholine, in the absence and presence of the endothelial NO synthase inhibitor N^G -monomethyl-L-arginine (L-NMMA), as well as responses to sodium nitroprusside were determined by plethysmography. The FBF response to acetylcholine was lower ($\sim 15\%$; $P < 0.05$) in the HFD group (4.5 ± 0.2 to 12.1 ± 0.8 mL/100 mL tissue/min) than in the LFD group (4.6 ± 0.2 to 14.4 ± 0.6 mL/100 mL tissue/min). L-NMMA significantly reduced the FBF response to acetylcholine in the LFD group ($\sim 25\%$) but not in the HFD group. There were no differences between groups in the vasodilator response to sodium nitroprusside. These data indicate that a high-fat diet is associated with endothelium-dependent vasodilator dysfunction due, in part, to diminished NO bioavailability. Impaired NO-

mediated endothelium-dependent vasodilation may contribute to the increased cardiovascular risk with high dietary fat intake.

Résumé

Une alimentation riche en gras est associée à un plus haut risque de maladie cardiovasculaire. Parmi les mécanismes potentiels à la base de ce haut risque de maladie cardiovasculaire, il y a la dysfonction de l'endothélium. La vasodilatation endothéliodépendante médiée par l'oxyde nitrique (NO) est essentielle à la régulation du tonus vasculaire et de la santé vasculaire globale. Cette étude se propose de déterminer l'effet de l'apport alimentaire en gras sur la vasodilatation endothéliodépendante. Quarante-quatre adultes d'âge mûr et d'adultes âgées, sédentaires et en bonne santé, participent à cette étude au cours de laquelle 24 parmi eux ont un apport alimentaire faible en gras (LFD; 29 ± 1 % des calories provenant du gras) et 20 autres, un apport riche en gras (HFD; 41 ± 1 % des calories provenant du gras). On utilise le carnet alimentaire de 4 jours pour évaluer l'apport en gras et on se réfère aux directives de l'AHA (*American Heart Association*) pour la classification (<35 % de toutes les calories provenant du gras). On évalue par la pléthysmographie le débit sanguin dans l'avant-bras (FBF) en réponse à l'acétylcholine, et ce, en présence et en l'absence de N^G -monométhyl-L-arginine (L-NMMA), un inhibiteur de la NO-synthase endothéliale et en réponse aussi au nitroprussiate de sodium. La FBF en réponse à l'acétylcholine est plus faible (~ 15 %; $P < 0,05$) dans le groupe HFD (de $4,5 \pm 0,2$ à $12,1 \pm 0,8$ mL/100 mL tissu/min) comparativement au groupe LFD (de $4,6 \pm 0,2$ à $14,4 \pm 0,6$ mL/100 mL tissu/min). L-NMMA suscite une diminution significative du FBF en réponse à l'acétylcholine dans le groupe LFD (~ 25 %), mais pas dans le groupe HFD. On n'observe pas de différences de vasodilatation entre les groupes en réponse au nitroprussiate de sodium. D'après ces observations, un apport alimentaire riche en gras est associé à une dysfonction de la vasodilatation endothéliodépendante causée en partie par la diminution de la biodisponibilité de NO. Une anomalie de la vasodilatation endothéliodépendante médiée par le NO pourrait contribuer à la hausse du risque de maladie cardiovasculaire en réponse à un apport élevé de gras alimentaire. [Traduit par la Rédaction]

Keywords

endothelium; vasodilation; high-fat diet; forearm blood flow; nitric oxide; cardiovascular disease

Mots-clés

endothélium; vasodilatation; régime riche en gras; débit sanguin dans l'avant-bras; oxyde nitrique; maladie cardiovasculaire

Introduction

The importance of diet in the prevention or development of cardiovascular disease (CVD) is well established. Dietary fat intake plays a particularly important role in cardiovascular health and disease (Bhupathiraju and Tucker 2011). Epidemiologic and clinical studies have demonstrated that plasma total cholesterol concentrations are strongly associated with the risk for coronary heart disease (Verschuren et al. 1995; Keys 1997) and that plasma

cholesterol levels are directly linked to dietary fat intake (Keys et al. 1957). Thus, modification of fat intake is a key strategy for reducing the development and progression of CVD (Vafeiadou et al. 2012). Early research evaluating the relation between dietary fat and CVD focused on lipoprotein abnormalities. More recent work indicates a potential role of vascular dysfunction with high dietary fat intake (Vogel et al. 1997). Indeed, postprandial lipemia due to high-fat meal ingestion has been shown to transiently impair endothelial function in adult humans (Vogel et al. 1997; Anderson et al. 2001).

Vascular endothelial function is essential to the maintenance of cardiovascular health. Impaired endothelial function, particularly impaired nitric oxide (NO)-mediated endothelium-dependent vasodilation, occurs early in the atherogenic process and contributes to the progression of atherosclerotic diseases and acute vascular events (Yasue et al. 1990; Vanhoutte et al. 2009). While the effects of acute dietary fat intake on flow-mediated vasodilation have been studied, the influence of habitual dietary fat intake on endothelial function is not clear. If high dietary fat intake is associated with diminished endothelium-dependent vasodilation, this may underlie the increased CVD risk with diets high in fat.

We tested the hypothesis that high dietary fat intake is associated with impaired endothelium-dependent vasodilation. To test this hypothesis, we used an isolated forearm model to determine blood flow response to acute intra-brachial infusions of endothelium dependent and independent vasoactive agents.

Materials and methods

Study population

Forty-four sedentary middle-aged and older adults (age range: 43–67 years) were studied: 24 (13 men, 11 women) with habitual dietary fat intake <35% of total calories (lower fat diet; LFD) and 20 (12 men, 8 women) with habitual dietary fat intake ≥35% of total calories (high-fat diet; HFD). Dietary fat intake classifications were based on American Heart Association (AHA) guidelines that recommend consuming <35% of total calories from fat (Eckel et al. 2014).

All subjects were screened for clinical evidence of CVD by medical history, physical examination, fasting blood chemistries, and electrocardiograms and blood pressure at rest and during incremental exercise performed to exhaustion. 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); or hypertension (arterial blood pressure ≥140/90 mm Hg). 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 fully explained to them before providing written, informed consent according to the guidelines of the University of Colorado at Boulder.

Measurements

Body composition—Body mass was measured to the nearest 0.1 kg using a medical beam balance (Detecto, Webb City, Mo., USA). Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Minimal waist circumference was measured according to published guidelines (Lohman et al. 1988).

Metabolic measurements—Fasting plasma lipid, lipoprotein, glucose, and insulin concentrations were determined using standard techniques as previously described (Van Guilder et al. 2008).

Dietary assessment—A bionutritionist at the University of Colorado Boulder Clinical and Translational Research Center instructed subjects 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 recording period. All completed dietary recall records were analyzed by the bionutritionist using The Food Processor nutrition analysis software (ESHA Research, Salem, Ore., USA).

Intra-arterial infusion studies—All measurements were performed in a temperature-controlled room between 0700 and 1000 after a 12-h overnight fast as previously described by our laboratory (Hoetzer et al. 2003). Briefly, a 5-cm, 20-gauge catheter was introduced into the brachial artery of the nondominant arm under local anesthesia (1% lidocaine). Forearm blood flow (FBF) was measured using strain-gauge venous occlusion plethysmography (D.E. Hokanson, Bellevue, Wash., USA). Following the measurement of resting blood flow for 5 min, acetylcholine was infused intra-arterially at rates of 4.0, 8.0, and 16.0 $\mu\text{g}/100\text{ mL tissue/min}$ and sodium nitroprusside was infused at rates of 1.0, 2.0, and 4.0 $\mu\text{g}/100\text{ mL tissue/min}$ for 5 min at each dose as previously described (Hoetzer et al. 2003). The sequence of drug administration was randomized to avoid an order effect.

In a subgroup of subjects, we determined the contribution of NO to acetylcholine-dependent vasodilation. In 12 of the 24 adults in the LFD group and 8 of the 20 in the HFD group, FBF responses to acetylcholine were determined before and after administration of the endothelial nitric oxide synthase (eNOS) inhibitor N^G -monomethyl-L-arginine (L-NMMA; Clinalfa, Laufelfingen, Switzerland). Owing to limited drug availability, FBF responses to acetylcholine + L-NMMA were not assessed in all subjects.

Statistical analysis—Differences in subject baseline characteristics and area under the curve data between groups were determined by analysis of variance (ANOVA). Between-group differences in FBF in response to acetylcholine, sodium nitroprusside, and the co-infusion of acetylcholine and L-NMMA were determined by repeated-measures ANOVA. Relations between variables of interest were assessed by linear regression analysis. Stepwise regression analysis was used when multiple variables of interest were correlated with outcome variables. There were no significant gender interactions; therefore, the data were pooled and are presented together. All data are expressed as means $\pm$ SE. Statistical significance was set a priori at $P < 0.05$.

Results

Selected subject characteristics are presented in Table 1. There were no significant differences between the groups in any anthropometric, hemodynamic, or metabolic variables and all values were within clinically normal ranges. Table 2 shows dietary macronutrient composition for the groups. There was no significant difference between groups in total caloric intake; however, the percentages of calories from fat (including saturated fat) and protein were higher and the percentage of calories from carbohydrates was lower in the HFD than the LFD group.

Resting FBF in the noninfused arm did not change throughout the infusion protocol (data not shown). FBF responses to acetylcholine and sodium nitroprusside are shown in Fig. 1. FBF responses to acetylcholine were approximately ~15% lower ($P < 0.05$) in the HFD group (from 4.5 ± 0.2 to 12.1 ± 0.8 mL/100 mL tissue/min) than in the LFD group (from 4.6 ± 0.2 to 14.4 ± 0.6 mL/100 mL tissue/min). As a result, the total blood flow response to acetylcholine (area under the curve) was significantly lower (~25%) in the HFD group (54 ± 6 mL/100 mL tissue) than in the LFD group (70 ± 5 mL/100 mL tissue). There were no significant differences in FBF responses to sodium nitroprusside between groups (Fig. 1).

In the subgroup that received L-NMMA, eNOS inhibition equally and significantly reduced resting FBF (~30%) in both the LFD (from 4.4 ± 0.3 to 3.0 ± 0.2 mL/100 mL tissue/min) and HFD (from 4.3 ± 0.3 to 3.0 ± 0.2 mL/100 mL tissue/min) groups. Co-infusion of L-NMMA with acetylcholine significantly reduced the vasodilator response to acetylcholine in the LFD but not the HFD group (Fig. 2). For example, at the peak dose of acetylcholine, FBF was ~25% lower ($P < 0.05$) with L-NMMA compared with acetylcholine alone in the LFD group (from 14.9 ± 0.9 to 11.5 ± 1.2 mL/100 mL tissue/min). In contrast, the peak FBF response to acetylcholine was not significantly affected by L-NMMA in the HFD group (from 12.1 ± 1.2 to 10.4 ± 0.3 mL/100 mL tissue/min).

In the overall study population, total fat intake ($r = -0.48$; $P < 0.05$) and carbohydrate intake ($r = 0.36$; $P < 0.05$) were inversely and positively associated, respectively, with the peak FBF response to acetylcholine. Stepwise regression analysis revealed that total fat ($R^2 = 0.23$) was the primary determinant of the vasodilator response to acetylcholine.

Discussion

The novel findings from the present study are as follows: (i) healthy adults who regularly consume a diet high in fat exhibit impaired endothelium-dependent vasodilation compared with adults who consume a diet that meets the AHA recommendations for fat intake; and (ii) the depression of endothelium-dependent dilation is due, in part, to diminished NO bioavailability. These results suggest that a habitual high-fat diet is associated with impaired NO-mediated endothelium-dependent vasodilation in middle-aged and older adults.

Diminished endothelium-dependent vasodilation, especially NO-mediated endothelial vasodilation, plays an early, prominent, and continuous role in atherogenesis (Vanhoutte et al. 2009). Endothelial vasodilator dysfunction is thought to underlie the increased cardiovascular risk associated with a diet high in fat. This postulate is based primarily on

data concerning the acute effects of high dietary fat intake (Plotnick et al. 1997; Vogel et al. 1997). Indeed, in a series of seminal studies, Vogel and colleagues (Plotnick et al. 1997, 2003; Vogel et al. 1997) demonstrated that a single high-fat meal (900 calories, 50 g of fat) acutely impaired flow-mediated dilation postprandially for up to 4 h in healthy, normocholesterolemic adults. The results of the present study significantly extend these findings by demonstrating that a habitual diet high in fat (> 35% of calories) is associated with markedly diminished NO-mediated endothelium-dependent vasodilation in middle-aged and older adults. The vasodilator response to the endothelial agonist acetylcholine was 20% lower, and the contribution of NO to the vasodilator response was negligible, in the subjects who reported regularly consuming a diet high in fat. Interestingly, while stimulated NO production was depressed in the high-fat diet group, basal production of NO was not affected. The reduction (~30%) in resting FBF in response to L-NMMA was identical between the groups. Determination of the reasons underlying this apparent diet-related discrepancy in NO production and/or release between basal and stimulated conditions in adult humans will require further study. Our findings contradict animal studies demonstrating high-fat diet-induced reductions in eNOS activity and NO production under basal conditions (Kim et al. 2008; Handa et al. 2011). Aside from the present study, we are aware of no other human studies directly assessing the effects of habitual high dietary fat intake on NO bioavailability. However, intact basal but impaired stimulated production or release of NO has been reported in other conditions (Weil et al. 2011a).

It is well documented that acetylcholine-mediated endothelium-dependent vasodilation is significantly lower in middle-aged and older adults than in young adults (DeSouza et al. 2000). In fact, the FBF responses to acetylcholine observed in the middle-aged and older adults in the present study are similar to previous findings from our laboratory in a separate cohort of subjects of similar age and health status (DeSouza et al. 2000). Although vasodilator capacity was already depressed, we observed a distinct negative influence of regular consumption of a high-fat diet on endothelial vasodilator function. Considering that most middle-aged and older adults in the United States consume a diet high in fat (Johnston et al. 2014), our findings provide further rationale for continued, persistent efforts to advocate lower fat diets in this already at-risk population. Future intervention studies are needed to determine whether reducing dietary fat intake in middle-aged and older adults who habitually consume a diet high in fat will concomitantly improve endothelium-dependent vasodilation.

The mechanisms underlying the dietary fat-related reduction in NO-mediated endothelium-dependent vasodilation are not clear. Aside from dietary composition, there were no significant differences between the groups in common anthropometric, metabolic, or hemodynamic factors that have been shown to adversely influence endothelium-dependent vasodilation, such as adiposity (Weil et al. 2011b), dyslipidemia (Casino et al. 1993), and hypertension (Panza et al. 1990). Thus, it appears that a regular high-fat diet may have a direct negative influence on the capacity of the endothelium to mediate vasodilation. Saturated fat intake has been implicated in promoting endothelial dysfunction; indeed, recent work by our group has demonstrated that endothelial fibrinolytic capacity is adversely influenced by saturated fat intake (Dow et al. 2014). In addition, others have shown that the type of fat (i.e., saturated, mono- or polyunsaturated) differentially affects endothelial cell

activation (De Caterina et al. 2000). Although we observed no correlation between endothelium-dependent vasodilation and type of fat consumed, we cannot dismiss this notion. The potential influence of trans fat on endothelium-dependent vasodilation is an interesting possibility. A diet high in trans fat has been linked to diminished flow-mediated dilation (de Roos et al. 2001) as well as endothelial cell activation and damage (Lopez-Garcia et al. 2005). Unfortunately, the ESHA software used in the present study to analyze dietary records does not quantify trans fat intake; as a result, we were unable to address this potential mechanism.

There are a few experimental considerations regarding this study that should be mentioned. First, because of the cross-sectional nature of this study, we cannot discount the possible influence of lifestyle and/or genetic factors on our results. However, to minimize the influence of lifestyle factors, we studied sedentary, nonsmoking adults of similar age and body composition who were not taking medications or supplements. Relatedly, we relied on 4-day food records to assess energy intake, which carries a potential self-reporting bias. However, 4-day food records have been shown to be an extremely reliable and reproducible tool for documenting and estimating energy intake (Basiotis et al. 1987). Indeed, written dietary records have been validated against weighed food records collected over a 1-year period (Bingham et al. 1994). Second, many other dietary factors (i.e., vitamins and minerals, phytochemicals, L-arginine, etc.) influence endothelial function (Brown and Hu 2001; Bhupathiraju and Tucker 2011). Unfortunately, we could not quantify intake of many of these dietary constituents using the ESHA software. Third, we cannot completely dismiss the possibility that our results may be due, at least in part, to the residual effects of the subject's last meal. However, all of the subjects were fasted for at least 10 h at the time of vascular testing, and the duration of impairment in flow-mediated dilation following a high-fat meal has been shown to be 4 to 6 h (Vogel et al. 1997). Therefore, we are confident that our findings represent the true endothelial phenotype associated with habitual consumption of a high fat-diet. Finally, we studied middle-aged and older adults and it is unknown whether a habitual diet high in fat is detrimental to vascular health in children or young adults.

In conclusion, the results of the present study demonstrate that habitual consumption of a diet high in fat (35% of total calories) is associated with impaired endothelium-dependent vasodilation due, in part, to diminished NO bioavailability. Endothelial vasodilator dysfunction may contribute to the increased risk of atherosclerotic vascular disease associated with a chronic diet predominately high in fat.

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Fig. 1. Forearm blood flow responses to (A) acetylcholine and (B) sodium nitroprusside in adults who habitually consume a lower fat or high-fat diet. Values are means $\pm$ SE. *, $P < 0.05$.

Fig. 2. Forearm blood flow responses to acetylcholine in the absence and presence of the nitric oxide synthase inhibitor *N*^G-monomethyl-L-arginine (L-NMMA) in adults who habitually consume a (A) lower fat or (B) high-fat diet. Values are means $\pm$ SE. *, $P < 0.05$.

Table 1

Selected subject characteristics.

Variable	Lower fat diet (n = 24)	High-fat diet (n = 20)
Men/women	13/11	12/8
Age, y	55±1	52±2
Body mass, kg	80.8±4.0	84.0±3.1
BMI, kg/m ²	27.3±1.2	27.7±0.9
Waist circumference, cm	91.4±3.4	95.1±2.6
Systolic BP, mm Hg	119±3	118±2
Diastolic BP, mm Hg	76±1	75±2
Total cholesterol, mg/dL	200.8±7.8	198.5±6.8
LDL-C, mg/dL	127.4±6.7	125.4±5.7
HDL-C, mg/dL	50.0±2.7	50.1±3.0
Triglycerides, mg/dL	117.1±11.3	114.9±14.0
Glucose, mg/dL	90.8±2.2	92.2±1.6
Insulin, µU/mL	6.1±0.7	6.8±0.9

Note: Values are means ± SE. BMI, body mass index; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Table 2

Dietary composition of the groups.

Variable	Lower fat diet (n = 24)	High-fat diet (n = 20)
Total kilocalories	2248±98	2357±121
Carbohydrates, %	49±1	39±2 *
Protein, %	15±1	17±1 *
Fat, %	29±1	41±1 *
Saturated fat, %	9±1	13±1 *
Monounsaturated fat, %	8±1	9±1
Polyunsaturated fat, %	4±1	5±1

Note: Values are means ± SE.* $P < 0.05$ vs. lower fat diet.