Meal-related increases in vascular reactivity are impaired in older and diabetic adults: insights into roles of aging and insulin in vascular flow

Michael R. Skilton,1 Nicole T. Lai,2 Kaye A. Griffiths,1 Lynda M. Molyneaux,3 Dennis K. Yue,1,3 David R. Sullivan,2 and David S. Celermajer1

1Department of Medicine, University of Sydney, and 2Department of Clinical Biochemistry and 3Diabetes Centre, Royal Prince Alfred Hospital, Camperdown, Australia

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Skilton, Michael R., Nicole T. Lai, Kaye A. Griffiths, Lynda M. Molyneaux, Dennis K. Yue, David R. Sullivan, and David S. Celermajer. Meal-related increases in vascular reactivity are impaired in older and diabetic adults: insights into roles of aging and insulin in vascular flow. Am J Physiol Heart Circ Physiol 288: H1404–H1410, 2005. First published October 28, 2004; doi:10.1152/ajpheart.00484.2004.—A fatty meal induces vasodilatation (of both resting and stimulated forearm flow) in healthy young adults, an effect most likely mediated by the vasodilator actions of insulin. We therefore hypothesized that an impaired meal-related vascular response might be an in vivo marker of vascular insulin resistance, related to the presence of diabetes and/or higher age. Postprandial vascular responses were assessed in three groups of subjects: 15 Type 2 diabetic subjects (age 58 ± 8 yr), 15 age-, gender-, and body mass index (BMI)-matched older control subjects (age 57 ± 9 yr), and 15 healthy young control subjects (age 33 ± 7 yr). Studies were carried out before and 3 and 6 h after a standardized high-fat meal (1,030 kcal, 61 g fat). Forearm microvascular flows were measured by strain gauge plethysmography and large-artery function by ultrasound. Resting blood flow and hyperemic area under curve (AUC) flow were not significantly different in diabetic subjects (resting 117 ± 42% and AUC 134 ± 46% of premeal values) compared with age-matched controls (resting 131 ± 39% and AUC 134 ± 47%); however, the response in diabetic subjects was blunted compared with young controls (resting 171 ± 67% and AUC 173 ± 99% of premeal values; P = 0.02 and P = 0.18, respectively). On multiple regression analysis, we found that increasing age (but not BMI or diabetes) was significantly associated with impaired postprandial vascular responses (resting: r = −0.4, P = 0.002; AUC: r = −0.4, P = 0.006). Therefore, meal ingestion results in impaired vaso dilator responses in older nondiabetic and diabetic adults, related to aging rather than insulin resistance.

Type 2 diabetes; insulin resistance

Vascular reactivity, determined in large part by endothelial and smooth muscle function, is impaired in early atherosclerosis (3). Furthermore, abnormal vascular reactivity, particularly impaired endothelial function, is an independent predictor of future coronary events (27, 31, 38). Most studies concerning vascular reactivity and the influence of risk factors (such as cholesterol, smoking, and diabetes) have been carried out in the fasting state (9). Humans, however, spend most of their waking hours in the postprandial state (1), and the effects of meals on vascular reactivity are relatively poorly understood.

We recently studied (29) the influence of a high-fat meal on vascular reactivity in healthy young adults, documenting a meal-related increase in both resting forearm blood flow (FBF) and ischemia-stimulated hyperemic FBF. These postprandial flow increases correlated with the rise in insulin levels and may have been due to the vasodilator effects of insulin.

As diabetes mellitus is characterized by peripheral insulin resistance (11), we hypothesized that diabetic adults might have impaired vasodilator responses after the ingestion of a fatty meal, compared with age-matched nondiabetic controls. Furthermore, as aging is a risk factor for both endothelial dysfunction and insulin resistance (6, 10, 14, 17), we also examined the effects of higher age on postprandial vascular reactivity.

METHODS

Subjects. We performed detailed small- and large-vessel studies, in the fasting and postprandial states, with 45 consecutively eligible adults comprising three predefined groups: 1) 15 clinically well subjects with Type 2 diabetes (1 subject aged 32 yr, others aged 50–65 yr), 2) 15 “older” control subjects who were healthy, not diabetic, and matched on a one-for-one sequential basis with the diabetic subjects for age (1 subject aged 29 yr, others 50–68 yr), gender, and body mass index (BMI), and 3) 15 healthy young control subjects (aged 20–42 yr). The Type 2 diabetes group had a glycosylated Hb (HbA1c) level of 6.8% (SD 0.3) and a clinically established diagnosis of diabetes for 4 yr (SD 1). There were nine men and six women in each group. All subjects were currently nonsmokers (for ≥6 mo) and had no known history of atherosclerotic or other cardiovascular disease. All vasoactive medications were withheld on the day of the study. Metformin was the only oral hypoglycemic agent permitted. Data for 11 of the 15 healthy young controls have been reported previously (29). This study was approved by the institutional ethics committee, and all subjects gave their written informed consent before participation in the study.

Study design. Subjects were tested in the fasting state (≥10 h overnight fast) and 3 and 6 h after eating a controlled fatty meal. At each of these three time points, small-vessel reactivity was tested by plethysmography and large-artery reactivity was assessed by ultrasound, as described below. The study meal, prepared by a dietician according to a standard recipe, consisted of two muffins, two portions of hash browns, a sausage, and a cheese slice, cooked in fresh tallow fat and had an energy content of 1,030 kcal (61 g fat; fatty acid profile: 48% saturated, 40% monounsaturated, 7.4% polysaturated, and 4.6% trans-fatty acids). All tests were undertaken in a quiet, temperature-controlled laboratory (22–24°C) while the subject rested in a supine position.

Plethysmography. FBF was measured by venous occlusion strain gauge plethysmography with calibrated mercury-in-Silastic strain gauges (Hokanson, Bellevue, WA). In each case, the forearm was supported at or above the level of the right atrium. The strain gauge...
was fixed around the portion of the left forearm with the greatest circumference. Circulation to the hand was prevented by inflating a cuff around the wrist to suprasystolic pressures (250 mmHg). Venous occlusion pressure averaged 60 mmHg in the cuff placed around the upper arm. Inflation of this cuff occluded the venous outflow from the distal portion of the arm without obstructing the arterial inflow. Under these conditions, the forearm circumference provides an accurate measure of changes in total microcirculatory volume (30), which accounts for the vast majority of the total volume of blood in the forearm.

Flow curves were recorded with a computer-based chart recorder (MacLab/8e System; ADInstruments, Castle Hill, Australia). Arterial inflow was measured by determining a straight regression line derived from the initial part of the upward flow curve during the first few pulses after upper arm cuff inflation (and the consequent venous outflow occlusion). The slope of that regression line reflects the forearm volume change per unit of time (ml/min · 100 ml tissue⁻¹).

After the resting blood flow measurements were completed (average of 6 acceptable flow curves), the upper arm cuff was inflated to a suprasystolic pressure (250 mmHg) for 5 min to induce forearm ischemia. After the pressure was released from the upper cuff, FBF was recorded for 100 s with an automated cuff controller. Blood flow was measured every 10–15 s from 5 to 100 s after cuff deflation. Postischemic hyperemia is common to most human vascular beds and is an indicator of the structural and functional vasodilator capacity of these tissues (22). Postischemic hyperemia is predominantly due to local metabolic factors such as lactic acid, prostaglandins, pH, adenosine, carbon dioxide, potassium, and nitric oxide (32). The ischemia-induced hyperemic area under the curve (AUC) volume was calculated as the area under the flow vs. time curve.

Ultrasound studies. Ultrasound assessment of brachial artery flow-mediated dilatation (FMD) was performed on the right arm. All studies were performed with a HDI5000 ultrasound mainframe (Philips, Bothell, WA) or equivalent, with a 12- to 5-MHz linear array transducer, as previously described (4, 5). Briefly, brachial artery diameter was measured from B-mode ultrasound images. The artery was scanned in longitudinal sections between 2 and 15 cm above the elbow. A resting scan was recorded, and arterial flow velocity was measured with a pulsed Doppler signal. Increased blood flow was induced by inflation of a blood pressure cuff placed around the forearm to a suprasystolic pressure of 250 mmHg for 4.5 min. A second scan was taken continuously from 30 s before until 90 s after cuff deflation, including a flow velocity measurement for the first 15 s after the cuff was released. After the hyperemic scan, 10–15 min was allowed for vessel recovery, and then a further resting scan was taken. At the end of each study day (6 h after the meal), a single 400-μg spray of sublingual nitroglycerin (glyceryl trinitrate spray, an endothelium-independent dilator) was administered after the FMD study, and 3–4 min later the last scan was acquired to assess nitrate-mediated dilatation.

Vessel diameter was measured by two independent observers who were blinded to the subject’s clinical details and the stage of the experiment, as previously described (4, 5). For the reactive hyperemia scan, diameter measurements were taken 45–60 s after cuff deflation. The vessel diameter in scans after reactive hyperemia and nitroglycerin administration was expressed as a percentage relative to the average diameter of the artery in the two resting (control) scans. This method was shown previously to be accurate and reproducible for measurement of small changes in arterial diameter, with low interobserver error for measurement of FMD and nitrate-induced arterial dilatation (5, 35).

Serum lipoproteins, insulin, and glucose. Total cholesterol and triglycerides were measured by standard enzymatic methods with a Hitachi 917 automatic analyzer. HDL cholesterol was measured directly with Roche reagents, and LDL cholesterol was calculated from the fasting blood sample by the Friedewald equation. Homocysteine was measured with high-pressure liquid chromatography as described previously (40). Insulin resistance was calculated based on the fasting insulin and fasting glucose with the homeostasis model assessment (HOMA).

Statistical methods. Descriptive data are expressed as means with SD in parentheses. Baseline characteristics were compared between groups with unpaired Student’s t-tests.

Repeated-measures ANOVA was performed for the blood flow parameters, insulin resistance, and glucose over time. Interactions were tested between time and group (younger group, older group, and diabetic subjects). Comparison between study groups of the effects of the fatty meal was also carried out by calculating both 3- and 6-h data as a percentage of premeal values and then analyzing with ANOVA. Spearman’s rank correlation coefficients were used to examine associations between pairs of measured parameters. Univariate regression analysis was used to test the association between potential independent predictors and changes in blood flow parameters. Backward stepwise regression was then performed to further quantify these associations. For this analysis, continuous data were assessed for normality and, if required, normalized with a log transformation. The variables included in the model were age (log transformation), BMI, gender, cholesterol, triglycerides, LDL, HDL (lipids were assessed as change from fasting values), lipoprotein (a), insulin resistance (HOMA), AUC glucose and insulin, and diabetic status (yes/no). Because of the possibility that the diabetic group had insulin deficiency, which can cause inaccurate measures of insulin resistance when assessed with HOMA, another model was constructed by replacing HOMA and AUC glucose and insulin with insulin-to-glucose ratio (values from relevant postmeal blood tests). Significant variables were included in the final model. Interactions between the dependent variables were also checked when necessary. Statistical significance was inferred at the 2P ≤ 0.05 level.

Regarding power calculations, our primary hypothesis was that there would be a significant difference in the postprandial hyperemic response in diabetic subjects compared with age-matched controls (as a result of hypothesized vascular insulin resistance in the diabetic subjects). On the basis of our previous work (29), we assumed a postprandial increase in hyperemic flow in non-diabetic controls of 70% (SD 25). Our study, with 15 diabetic subjects and 15 non-diabetic control subjects, was designed to have >80% power to detect a significant difference in this parameter between groups, at the 2P < 0.05 significance level, assuming a diabetes-related decrease of 40% in the postprandial vasodilator response.

Statistical analyses were performed with SPSS (version 9.0; Chicago, IL), NCSS97 (Number Cruncher Statistical System;Hintze J., Kaysville, UT) and SAS (version 6.12; SAS Institute) software.

RESULTS

Demographic data for the study subjects are shown in Table 1. Briefly, the young control group had a mean age of 33 ± 7

<table>
<thead>
<tr>
<th>Table 1. Characteristics of study population</th>
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<tr>
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<tr>
<td>Gender, male/female</td>
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<tr>
<td>Age, yr</td>
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<tr>
<td>BMI, kg/m²</td>
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<tr>
<td>Total cholesterol, mmol/l</td>
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<td>LDL cholesterol, mmol/l</td>
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<td>HDL cholesterol, mmol/l</td>
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<td>Lipoprotein (a), mg/l</td>
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<tr>
<td>Lipid-lowering medication, yes/no</td>
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<td>Metformin use, yes/no</td>
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Values for age, body mass index (BMI), cholesterol, and lipoprotein (a) are means with SD in parentheses; n = 15 subjects.
The Type 2 diabetes group displayed both an increased fasting glucose (P = 0.002 vs. older controls, P < 0.0001 vs. young controls) and a significant postprandial rise in glucose levels compared with both control groups (P = 0.006 vs. older controls, P = 0.001 vs. young controls; see Fig. 1). Additionally, there were significant differences in fasting total cholesterol and LDL cholesterol between the Type 2 diabetes subjects and the older controls (total cholesterol P = 0.007, LDL cholesterol P = 0.008). The postprandial rise in insulin was significantly greater in Type 2 diabetic subjects compared with the young controls (3 h, P = 0.08; 6 h, P = 0.02; see Fig. 1) but not compared with the older controls.

The postprandial rise in resting FBF after 3 h was significantly lower in the Type 2 diabetic group compared with the young control group (FBF as % of premeal value: 117% (SD 42) vs. 171% (SD 67) in diabetic subjects and young controls, respectively; P = 0.02) but not compared with the older controls (131% (SD 39), P = 0.37; see Fig. 2). Similarly, the meal-related change in hyperemic FBF tended to be lower in the diabetic group compared with the healthy young subjects, although not significantly so (3 h: 134% (SD 46) vs. 173% (SD 99) in diabetics and young subjects, respectively; P = 0.18), and was similar to the older controls (3 h: 134% (SD 47) for older subjects, P = 0.99 vs. diabetic subjects; see Fig. 2). The changes in FMD did not differ from either the young

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**Table 2. Vascular and blood results before and after consumption of a fatty meal**

<table>
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<tr>
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<th>Diabetic Subjects</th>
<th>Older Control Subjects</th>
<th>Young Control Subjects</th>
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<tbody>
<tr>
<td></td>
<td>Premeal</td>
<td>3 h after meal</td>
<td>6 h after meal</td>
</tr>
<tr>
<td>Glucose mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%Premeal value</td>
<td>7.3 (1.6)</td>
<td>10.0 (4.3)</td>
<td>6.8 (1.9)</td>
</tr>
<tr>
<td>Insulin pmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%Premeal value</td>
<td>56 (26)</td>
<td>338 (193)</td>
<td>113 (59)</td>
</tr>
<tr>
<td>Triglycerides mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%Premeal value</td>
<td>1.4 (0.7)</td>
<td>2.5 (1.4)</td>
<td>2.6 (2.1)</td>
</tr>
<tr>
<td>Resting FBF mL/min^-1-100 mL tissue^-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%Premeal value</td>
<td>1.6 (0.4)</td>
<td>1.8 (0.6)</td>
<td>1.9 (0.8)</td>
</tr>
<tr>
<td>Hyperemic FBF</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>mL/min^-1-100 mL tissue^-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%Premeal value</td>
<td>6.1 (3.0)</td>
<td>7.9 (4.5)</td>
<td>7.7 (4.5)</td>
</tr>
<tr>
<td>FMD, %</td>
<td>3.7 (2.2)</td>
<td>3.5 (3.2)</td>
<td>3.3 (2.9)</td>
</tr>
</tbody>
</table>

Values are means with SD in parentheses. FBF, forearm blood flow; FMD, flow-mediated dilatation.
controls (3 h, $P = 0.82$; 6 h, $P = 0.55$) or older controls (3 h, $P = 0.304$; 6 h, $P = 0.748$).

**Older controls.** All fasting values for both blood tests and measures of vascular function were similar in the healthy older subjects compared with the young controls (see Table 2). Furthermore, the meal-induced changes in insulin and triglyceride levels were not significantly different from those measured in the young controls.

Three hours after the meal, the older controls exhibited FBF increases of 131% (SD 39) and 134% (SD 47) for resting and hyperemic flow, respectively, compared with 171% (SD 67) and 173% (SD 99) for the young subjects. These differences were not statistically significant (resting $P = 0.06$, hyperemic $P = 0.18$). Likewise, 6 h after the meal, the incremental FBF response was less than in the young controls, but not significantly so [resting FBF: young controls 161% vs. older controls 127% ($P = 0.31$); hyperemic FBF: young controls 131% vs. older controls 122% increase ($P = 1.00$)].

**Young controls.** Serum glucose levels were not significantly different from the fasting values at either the 3- or 6-h time points. Insulin levels were significantly increased 3 h after the meal compared with fasting levels ($P = 0.001$). Serum triglycerides were significantly higher at both postmeal time points compared with fasting values (3 h, $P = 0.001$; 6 h, $P = 0.03$). FBF was increased by the fatty meal. Both resting and hyperemic values were significantly greater after 3 h (resting $P = 0.001$, hyperemic $P = 0.03$), but only resting FBF remained significantly higher at the 6-h postmeal time point (resting $P = 0.01$, hyperemic $P = 0.126$).

Regarding FMD, baseline (premeal) values were greater than in the older controls and the diabetic subjects (as seen in Table 2), but this was not statistically significant ($P = 0.19$ by ANOVA). As in the older diabetic and nondiabetic subjects, FMD was not altered by the meal in the healthy young nondiabetic subjects (3 h, $P = 0.539$; 6 h, $P = 0.252$ compared with premeal values; Table 2).

**Regression analyses.** Considering all 45 subjects together, parameters significantly associated with higher resting blood flow in the fasting state were higher fasting glucose ($P = 0.02$) and male gender ($P = 0.03$). Regarding associations of postprandial flows (Table 3), age and the percent change in triglycerides after the meal were significant predictors of the changes in both resting and hyperemic FBF at 3 h. Indeed, higher age was significantly associated with both reduced 3-h baseline FBF ($r = -0.41, P = 0.005$) and reduced 3-h hyperemic FBF ($r = -0.35, P = 0.019$); these results were similar when only the 30 nondiabetic subjects were considered. BMI was negatively correlated with the change in hyperemic FBF.

Backward stepwise regression confirmed that age was the best predictor of the change in resting and hyperemic FBF 3 h after the meal (resting: $r = -0.4, P < 0.001$; hyperemic: $r = -0.4, P = 0.006$; Fig. 3). Other factors significantly but more weakly influencing the meal-related changes in resting blood flow after 3 h included the AUC insulin ($r = 0.09, P = 0.02$). Insulin resistance, as assessed by the HOMA method, was weakly associated with the change in resting FBF after 3 h ($r = -0.09, P = 0.08$). When the insulin-to-glucose ratio was included in the model, the significant relationships with age remained, but the insulin-to-glucose ratio was also significantly correlated with the change in resting blood flow at 3 h ($r = 0.4, P = 0.007$).
In this study, we have shown that the increase in FBF in response to a fatty meal is diminished in older but otherwise healthy nondiabetic subjects compared with young nondiabetic controls. This postprandial vasodilator response was not further impaired in the presence of Type 2 diabetes. Furthermore, multiple regression analysis showed that aging was the predominant factor leading to impaired FBF after a fatty meal in both the resting and stimulated states.

Our study was designed to have sufficient power (≥80%) to detect a significant impairment in the postprandial vasodilator response in the diabetic subjects compared with age-matched controls (hypothesized because of insulin resistance in the vasculature). Despite this, the major finding of our study is that higher age, rather than the presence of diabetes mellitus, is associated significantly with an impaired vasodilator response after a fatty meal.

Aging is a major risk factor for cardiovascular disease (24), and, like other major risk factors, aging is associated with changes in preclinical markers of vascular health. With increasing age, the coronary arteries display an impaired response to endothelium-dependent vasodilators (14). Both the peripheral conduit arteries and the peripheral resistance vessels also manifest abnormal responses to endothelium-dependent stimuli in older subjects (6, 19). In our previous study (6) of 238 nondiabetic adults, aging was associated with a significant decrease in conduit artery endothelial function, measured as FMD, of −0.08%/yr (95% CI −0.04 to −0.12; P < 0.005). In the current study, which was not powered to detect age-related changes in FMD with only 30 nondiabetic adults, the average annual change in FMD was −0.05%, consistent with our previous findings in the larger study (6), although not statistically significant for this secondary end point of the present study.

Here, we extend these previous findings by showing that aging is also associated with an impaired meal-related vasodilatation of the forearm microcirculation, even after adjusting for baseline flow values. Because of the large proportion of time spent in the postprandial state, this age-related impaired response may be an important component of the pathophysiology of cardiovascular disease.

Proposed mechanisms for the impaired vasodilator response of the vasculature with aging include a decreased release of endothelium-derived relaxing factor, increased release of vasoconstrictors, and an increase in the degradation of nitric oxide by oxygen-derived free radicals (14, 19). The relative importance of nitric oxide in determining vascular reactivity in general does appear to differ, however, between the large arteries and the microcirculation (21, 32). There is also evidence for altered vascular responses to prostanoids with aging (33).

Although the majority of research examining the links between cardiovascular risk factors and vascular function is conducted in the fasting state, there is an emerging body of...
literature suggesting that abnormal changes in metabolic parameters and vascular function after a meal may be important. Because most humans spend the majority of their waking hours in the postprandial state, any proatherogenic changes that occur in response to a meal could have a disproportionate influence on cardiovascular health and subsequent risk of developing atherosclerosis.

In Type 2 diabetes, there is an impaired ability to control both serum glucose and triglycerides after the consumption of a meal. This may contribute to the increased cardiovascular risk in these subjects (20, 36). The nutritional components of a meal also affect the physiological postprandial response (26); however, to study a characteristic Western-style high-fat diet, a fatty meal is commonly used. Hypertriglyceridemia along with obesity and endothelial dysfunction have been proposed as mechanisms linking a characteristic Western-style high-fat diet with cardiovascular disease.

Fasting homocysteine has been shown to be associated with atherosclerosis (8), possibly via a nitric oxide-associated pathway (37). Although methionine-induced mild hyperhomocysteinemia has been shown to transiently impair endothelial function in older subjects (7), it is not related to either micro- or macrovascular complications in diabetic patients (34). In our study, meal-related changes in homocysteine levels were not significantly associated with the magnitude of the postprandial vasodilator responses.

The effect of a fatty meal on endothelial function, however, is contentious. In this current study, endothelial function, assessed with brachial artery flow-mediated dilatation, was preserved after the meal in all groups. This is consistent with both our previous findings (29) and those of some studies in healthy young adults (12, 13). However, this is contrary to other findings that have shown that a fatty meal transiently impairs endothelial function (2, 41), putatively via hypertriglyceridemia-enhanced oxidative stress (2, 16, 18, 28). Study limitations. The aim of this study was to examine postprandial vascular responses rather than to confirm our (and other) previous observations regarding the significant impairment in fasting endothelial function, known to be associated with diabetes and with higher age (6, 14, 15, 19, 25). Thus, although we observed no significant difference in resting large-artery endothelial function between groups in this study, the magnitude of age-related change in FMD was consistent with our previous observations derived from much larger numbers of nondiabetic subjects (6).

We also observed a large variability in postmeal vascular responses between the subjects within each group. Similar large interindividual variabilities in the vasoactive properties of insulin have been observed consistently by others (23, 39). Thus, it is possible that some significant associations might not have been detected because of type 2 error, even though the study was well powered for testing the primary hypotheses.

To assist the comparison with our previous study examining the effects of a fatty meal on FBF, we chose the same time points for postprandial blood and vascular reactivity tests (at 3 and 6 h after the meal). Although continuous or more frequent postprandial measurements might have been informative, this would be logistically difficult and might risk “vascular fatigue” in subjects having repeated and frequent hyperemia measurements.

Our primary study hypothesis, that diabetes would be associated with impaired postprandial vascular responses because of a putative “vascular insulin resistance,” was not supported by the data. Rather, we observed (on group comparison and regression analyses) that higher age was significantly associated with reduced postprandial vascular flow responses. By study design, however, there was a slight overlap in age between groups, in that one “older control,” matched for a younger subject with Type 2 diabetes, was actually within the range of the young control group. Other than this one subject, the younger and older controls were clearly separated by age (20–42 vs. 50–68 yr). The relationship between higher age and reduced postprandial forearm flows were robust, even with inclusion of this single younger “old control,” and were not significantly changed by exclusion of this individual.

In conclusion, we have shown in the present study that the normal physiological vasodilator responses of the forearm microcirculation in response to a fatty meal are diminished in older but otherwise healthy control subjects. This response was not further impaired in the presence of Type 2 diabetes. Furthermore, regression analysis showed that aging was the predominant factor leading to impaired FBF after a fatty meal, rather than resistance to insulin, in both the resting and stimulated states.

GRANTS

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