Meal-Related Increases in Vascular Reactivity are Impaired in Older and Diabetic Adults - Insights into the Roles of Aging and Insulin in Vascular Flow

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Running head: Aging impairs post-prandial vasodilatation

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Abstract

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 older age. Post-prandial vascular responses were assessed in three groups of subjects; fifteen type 2 diabetic subjects (age 58 ± 8yrs), 15 age, gender and BMI-matched older controls (age 57 ± 9 years), and 15 healthy young controls (age 33 ± 7yrs). Studies were carried out before, 3 and 6 hours after a standardized high-fat meal (1030 kcal, 61g fat). Forearm microvascular flows were measured using strain-gauge plethysmography and large artery function by ultrasound. Resting blood flow and hyperemic “area under curve” (AUC) flow were not significantly different in the diabetic subjects (resting 117 ± 42% & AUC 134 ± 46% of pre-meal values) compared with the age-matched controls (resting 131 ± 39% & AUC 134 ± 47%, p = NS), however the response in the diabetics was blunted when compared with young controls (resting 171 ± 67% & AUC 173 ± 99% of pre-meal 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 post-prandial vascular responses (resting: r = -0.4, p = 0.002; AUC: r = -0.4, p = 0.006). Therefore meal ingestion results in impaired vasodilator responses in older non-diabetic and diabetic adults, related to aging rather than insulin resistance.

Keywords: Aging, type 2 diabetes, insulin resistance, vascular reactivity
Introduction

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 post-prandial state,(1) and the effects of meals on vascular reactivity are relatively poorly understood.

We recently studied 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 and ischemia-stimulated hyperemic flow.(29) These post-prandial 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,(12) we hypothesized that diabetic adults might have impaired vasodilator responses after the ingestion of a fatty meal, compared with age-matched non-diabetic controls.

Furthermore, as ageing is a risk factor for both endothelial dysfunction and insulin resistance,(6, 11, 14, 17) we also examined the effects of older age on post-prandial vascular reactivity.
Methods

Subjects. We performed detailed small and large vessel studies, in the fasting and post-prandial state, in 45 consecutively eligible adults comprising three predefined groups; (i) 15 clinically well subjects with type 2 diabetes (one subject aged 32 years, others aged 50-65 years), (ii) 15 “older” controls who were healthy, not diabetic and matched in a one-for-one, sequential basis with the diabetic subjects for age (one subject aged 29 years, others 50-68 years), gender and body mass index (BMI), and (iii) 15 healthy young controls (aged 20-42 years). The type 2 diabetes group had HbA1c of 6.8 ± 0.3% and a clinically established diagnosis of diabetes for 4 ± 1 years. There were 9 men and 6 women in each group. All subjects were current non-smokers (for ≥ 6 months) 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 has been previously reported.(29) This study was approved by the institutional ethics committee, and all subjects gave their written informed consent prior to participation in the study.

Study design. Subjects were tested in the fasting state (≥ 10 hour overnight fast), 3 hours after and 6 hours after eating a controlled fatty meal. At each of these 3 time points, small vessel reactivity was tested by plethysmography and large artery reactivity assessed by ultrasound, as described below. The study meal was prepared by a dietician according to a standard recipe and consisted of two muffins, two hash browns, a sausage and a cheese slice, cooked in fresh tallow fat and had an energy content of 1030 kcal (61g fat, fatty acid profile: 48% saturated, 40% monounsaturated, 7.4% polyunsaturated and 4.6% trans fatty acids). All tests were undertaken in a quiet, temperature-controlled laboratory (22-24ºC), while the subject rested in a supine position.
**Plethysmography.** Forearm blood flow (FBF) was measured by venous occlusion strain-gauge plethysmography, using calibrated mercury-in-silastic strain gauges (Hokanson, Bellevue, Washington). 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 (250mmHg). Venous occlusion pressure averaged 60mmHg in the cuff placed around the upper arm. Inflation of this cuff occludes 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 using 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/100ml tissue).

After completing the resting blood flow measurements (average of six acceptable flow curves), the upper arm cuff was inflated to a suprasystolic pressure (250mmHg) for 5 minutes to induce forearm ischemia. After releasing the pressure from the upper cuff, the FBF was recorded for 100 seconds by using an automated cuff controller. Blood flow was measured every 10-15 seconds from 5 to 100 seconds 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 curve” (AUC) volume was calculated as the area under the flow vs time curve.

Ultrasound studies. The ultrasound assessment of brachial artery flow-mediated dilatation (FMD) was performed on the right arm. All studies were performed using a HDI5000 ultrasound mainframe (Philips, Bothell, WA) or equivalent, with a 12-5 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 using 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 minutes. A second scan was taken continuously from 30 seconds before, until 90 seconds after cuff deflation, including a flow velocity measurement for the first 15 seconds after the cuff was released. After the hyperemic scan, 10 to 15 minutes was allowed for vessel recovery, and then a further resting scan was taken. At the end of each study day (6 hours after the meal), a single 400µg spray of sublingual nitroglycerin (glyceryl trinitrate spray, an endothelium independent dilator) was administered after the FMD study, and 3 to 4 minutes 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 stage of the experiment, as previously described.(4, 5) For the reactive hyperemia scan, diameter measurements were taken 45 to 60 seconds 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 has been previously shown 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, using a Hitachi 917 automatic analyzer. HDL cholesterol was measured directly using Roche reagents, and LDL cholesterol was calculated from the fasting blood sample using the Friedewald equation. Homocysteine was measured using high-pressure liquid chromatography as described previously.\(^{(40)}\) Insulin resistance was calculated based on the fasting insulin and fasting glucose using the homeostasis model assessment (HOMA).

**Statistical methods.** Descriptive data are expressed as mean ± SD. Baseline characteristics were compared between groups using unpaired students t-tests. Repeated measures analysis of variance 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 hour data as a percentage of pre-meal values and then analyzed using 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 using 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), Lp(a), insulin resistance (HOMA), area under the curve glucose & insulin, and diabetic status (yes/no). Due to the possibility that the diabetic group had insulin
deficiency, which can cause inaccurate measures of insulin resistance when assessed using HOMA, another model was also constructed by replacing HOMA and area under the curve glucose & insulin, with the insulin/glucose ratio (values from relevant post-meal 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 2p ≤ 0.05 level.

Regarding power calculations, our primary hypothesis was that there would be a significant difference in the post-prandial hyperemic response in diabetic subjects, compared with age-matched controls (as a result of hypothesized vascular insulin resistance in the diabetic subjects). Based on our previous work,(29) we assumed a post-prandial increase in hyperemic flow in non-diabetic controls of 70 ± 25%. Our study, with 15 diabetic subjects and 15 non-diabetic controls, 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 post-prandial vasodilator response.

Statistical analyses were performed using SPSS Software (version 9.0, Chicago, USA), NCSS97 (Number Cruncher Statistical System, Hintze J. 1999) and SAS (version 6.12, SAS Institute Incorporated) 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 years and BMI of 24.6 ± 3.3 kg/m². Older controls and diabetics had a higher age (57 ± 9 and 58 ± 8 years respectively, both p < 0.0001 vs young controls) but not BMI (26.3 ± 3.5 kg/m², p = 0.20; and 27.4 ± 5.0, p = 0.74), compared with the younger controls.

Results of blood tests and measures of vascular function are shown in table 2. Additionally, fasting homocysteine was significantly higher in both the diabetic group (13.2 ± 7.1 µmol/l, p = 0.01 vs young controls) and older controls (10.3 ± 3.4 µmol/l, p = 0.05 vs young controls), when compared with the young controls (8.1 ± 2.3 µmol/l).

There were no differences between groups in the meal-related change in homocysteine level.

Type 2 Diabetic 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 figure 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 diabetics than in the young controls (3hr, p = 0.08; 6hr, p = 0.02; see figure 1), but not compared with the older controls.

The postprandial rise in resting FBF after 3 hours was significantly lower in the type 2 diabetic group than in the young control group (FBF as a % of pre-meal value: 117 ± 42% vs 171 ± 67% in diabetics and young controls respectively, p = 0.02), but not compared with the older controls (131 ± 39%, p = 0.37, see figure 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 hours: 134 ± 46% vs 173 ± 99% in diabetics and young subjects respectively, p = 0.18), and was similar to the older controls (3 hours: 134 ± 47% for older subjects, p = 0.99 vs diabetics; see figure 2).

The changes in FMD did not differ from either the young controls (3hr p = 0.82, 6hr p = 0.55) or older controls (3hr p = 0.304, 6hr p = 0.748).

**Older Controls.** All fasting values for both blood tests and measures of vascular function were similar in the healthy older subjects when 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 ± 39% and 134 ± 47% for resting and hyperemic flow respectively, compared with 171 ± 67% and 173 ± 99% for the young subjects. These differences were not statistically significant (resting p = 0.06, hyperemic p = 0.18). Likewise, six hours 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 hour timepoints. Insulin levels were significantly increased 3 hours after the meal compared with fasting levels (p = 0.001). Serum triglycerides were significantly higher at both post-meal timepoints, compared with fasting values (3hr p = 0.001, 6hr p = 0.03). FBF was increased by the fatty meal. Both resting and hyperemic values were significantly greater after 3 hours (resting: p
= 0.001; hyperemic: p = 0.03), but only resting FBF remained significantly higher at the 6 hour post-meal timepoint (resting: p = 0.01; hyperemic: p = 0.126).

Regarding FMD, baseline (pre-meal) 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 non-diabetic subjects, FMD was not altered by the meal, in the healthy young non-diabetic subjects (3hr p = 0.539, 6hr p = 0.252 compared with pre-meal 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 post-prandial flows (table 3), age and the percentage change in triglycerides after the meal were significant predictors of both the changes in resting and hyperemic FBF at 3 hours. Indeed, older age was significantly associated with both reduced 3 hour baseline FBF (r = -0.41, p = 0.005) as well as reduced 3 hour hyperemic FBF (r = -0.35, p = 0.019); these results were similar when only the 30 non-diabetic subjects were considered. BMI was negatively correlated with the change in hyperemic FBF. Backward step-wise regression confirmed that age was the best predictor of the change in resting and hyperemic FBF 3 hours post-meal (resting: r = -0.4, p < 0.001; hyperemic: r = -0.4, p = 0.006; figure 3). Other factors significantly but more weakly influencing the meal-related changes in resting blood flow after 3 hours included the AUC insulin (r = 0.09, p = 0.02). Insulin resistance, as assessed using the HOMA method, was weakly associated with the change in resting FBF after 3 hours (r = -0.09, p = 0.08). When the insulin/glucose ratio was included in the model, the significant relationships with age remained, but the insulin/glucose ratio was also significantly correlated with the change in resting blood flow at 3 hours (r = 0.4, p = 0.007).
Discussion

In this study, we have shown that the increase in forearm blood flow in response to a fatty meal is diminished in older but otherwise healthy non-diabetic subjects, compared with young non-diabetic controls. This post-prandial 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 forearm blood flow after a fatty meal, both in the resting and stimulated states.

Our study was designed to have sufficient power (>80%) to detect a significant impairment in the post-prandial vasodilator response in the diabetic subjects, compared with age-matched controls (hypothesized due to insulin resistance in the vasculature). Despite this, the major finding of our study is that older 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 peripheral resistance vessels also manifest abnormal responses to endothelium dependent stimuli, in older subjects.(6, 19) In our previous study of 238 non-diabetic adults, aging was associated with a significant decrease in conduit artery endothelial function, measured as FMD, of −0.08% per year (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 non-diabetic 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 endpoint of the current report.
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. Due to the large proportion of time spent in the post-prandial 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.\(^{(33)}\)

While 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. As most humans spend the majority of their waking hours in the postprandial state, any pro-atherogenic 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 will also affect the physiological post-prandial 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) While methionine-induced mild hyperhomocysteinemia has been shown to transiently impair endothelial function in older subjects,(7) it is not related to either micro- or macro-vascular complications in diabetics.(34) In our study, meal-related changes in homocysteine levels were not-significantly associated with the magnitude of the post-prandial vasodilator responses.

The effect of a fatty meal on endothelial function, however, is contentious. In this current study, endothelial function, assessed using brachial artery flow-mediated dilatation, was preserved post-meal in all groups. This is consistent with both our previous findings and those of some studies in healthy young adults.(10, 13, 29) However this is contrary to other findings, which 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 post-prandial 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 older age.(6, 14, 15, 19, 25) Thus, while 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 non-diabetic subjects.(6) We also observed a large variability in post-meal vascular responses, between the subjects within each group. Similar large inter-individual variabilities to the vasoactive properties of insulin have been consistently observed by others.(23, 39) Thus it is possible that some significant associations might not have been detected due to 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 post-prandial blood and vascular reactivity tests (at 3 and 6 hours post-meal). Although continuous or more frequent post-prandial measurements may 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 post-prandial vascular responses due to a putative “vascular insulin resistance”, was not supported by the data. Rather, we observed (on group comparison and regression analyses) that older age was significantly associated with reduced post-prandial 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 for this one subject, the younger and older controls were clearly separated by age (20-42 vs 50-68 years). The relationship between older 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.

**Conclusions.** In this study, we have shown that the normal physiologic 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 forearm blood flow after a fatty meal, rather than resistance to insulin, in both the resting and stimulated states.
Grants

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References


30. **Roberts DH, Tsao Y, and Breckenridge AM.** The reproducibility of limb blood flow measurements in human volunteers at rest and after exercise by using


37. **Stamler JS, Osborne JA, Jaraki O, Rabbani LE, Mullins M, Singel D, and Loscalzo J.** Adverse vascular effects of homocysteine are modulated by endothelium-


**Figure Legends**

Figure 1. a) Glucose and b) Insulin levels throughout the duration of the study day. Type 2 diabetics (▲), older controls (■) and young controls (○).

Figure 2. Effects of a fatty meal on resting and hyperemic forearm blood flow in a) type 2 diabetic subjects, b) older controls, and c) young controls. Pre-meal (○), 3 hours post-meal (■), and 6 hours post-meal (▲). Resting and hyperemic flow displayed as measured timepoints.

Figure 3. Association between age and increase in a) resting forearm blood flow (FBF), and b) hyperemic FBF three hours after a fatty meal. FBF is displayed as a percentage of the pre-meal resting FBF.
Table 1. Characteristics of study population. Mean ± SD unless otherwise stated.

<table>
<thead>
<tr>
<th></th>
<th>Type 2 diabetics (n=15)</th>
<th>Older controls (n=15)</th>
<th>Young controls (n=15)</th>
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<td>Gender (M/F)</td>
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<td>9/6</td>
<td>9/6</td>
</tr>
<tr>
<td>Age - years</td>
<td>58 ± 8</td>
<td>57 ± 9</td>
<td>33 ± 7</td>
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<tr>
<td>BMI – kg/m²</td>
<td>27.4 ± 5.0</td>
<td>26.3 ± 3.5</td>
<td>24.6 ± 3.3</td>
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<tr>
<td>Total Cholesterol – mmol/l</td>
<td>4.8 ± 0.6</td>
<td>5.8 ± 1.0</td>
<td>5.1 ± 0.8</td>
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<td>LDL Cholesterol – mmol/l</td>
<td>3.6 ± 0.9</td>
<td>2.7 ± 0.5</td>
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<td>HDL Cholesterol – mmol/l</td>
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<td>1.5 ± 0.4</td>
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<td>Lipoprotein (a)</td>
<td>220 ± 187</td>
<td>209 ± 213</td>
<td>121 ± 139</td>
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<tr>
<td>Lipid-lowering medication (Y/N)</td>
<td>3/12</td>
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</tr>
<tr>
<td>Metformin use (Y/N)</td>
<td>10/5</td>
<td>0/15</td>
<td>0/15</td>
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Table 2. Vascular and blood results before, 3 hours after and 6 hours after the consumption of a fatty meal. Values are means ± SD.

<table>
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<th>Diabetic Subjects</th>
<th>“Older” Controls</th>
<th>Young Controls</th>
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<tr>
<td></td>
<td>Pre-meal 3 hrs post 6 hrs post Pre-meal 3 hrs post 6 hrs post Pre-meal 3 hrs post 6 hrs post</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose – mmol/l (% pre-meal value)</td>
<td>7.3 ± 1.6 (135 ± 40) 6.8 ± 1.9 (98 ± 27) 5.5 ± 0.6 (103 ± 16) 5.3 ± 0.6 (97 ± 8) 5.3 ± 0.4 (95 ± 13) 5.0 ± 0.6 (95 ± 12)</td>
<td></td>
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<tr>
<td>Insulin – pmol/l (% pre-meal value)</td>
<td>56 ± 26 (703 ± 594) 113 ± 59 (223 ± 107) 49 ± 26 (524 ± 384) 82 ± 64 (159 ± 68) 51 ± 30 (350 ± 156) 76 ± 91 (133 ± 80)</td>
<td></td>
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</tr>
<tr>
<td>Triglycerides – mmol/l (% pre-meal value)</td>
<td>1.4 ± 0.7 (169 ± 36) 2.6 ± 2.1 (174 ± 73) 1.4 ± 0.6 (200 ± 69) 2.9 ± 1.5 (208 ± 64) 1.1 ± 0.5 (192 ± 65) 1.7 ± 1.4 (145 ± 49)</td>
<td></td>
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<tr>
<td>Resting FBF – ml/min/100ml tissue (% pre-meal value)</td>
<td>1.6 ± 0.4 (117 ± 42) 1.9 ± 0.8 (119 ± 51) 1.5 ± 0.5 (131 ± 39) 1.8 ± 0.6 (127 ± 35) 1.4 ± 0.5 (171 ± 67) 2.0 ± 0.8 (161 ± 74)</td>
<td></td>
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<tr>
<td>Hyperemic FBF – ml/100ml tissue (% pre-meal value)</td>
<td>6.1 ± 3.0 (134 ± 46) 7.9 ± 4.5 (125 ± 46) 7.7 ± 4.5 (134 ± 47) 7.8 ± 2.6 (122 ± 51) 6.0 ± 2.9 (173 ± 99) 7.2 ± 4.7 (131 ± 50)</td>
<td></td>
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<tr>
<td>FMD - %</td>
<td>3.7 ± 2.2 3.5 ± 3.2 3.3 ± 2.9 3.2 ± 2.9 4.2 ± 2.7 2.5 ± 2.7 4.5 ± 3.3 4.0 ± 4.2 3.4 ± 3.0</td>
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Table 3. Determinants of the changes in a) resting, and b) hyperemic forearm blood flow 3 hours after versus before a fatty meal; results of univariate regression analyses.

### a)

<table>
<thead>
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<th></th>
<th>$R^2$</th>
<th>$\beta$ regression coefficient</th>
<th>p-value</th>
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<tr>
<td>$\Delta$ Triglycerides</td>
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<tr>
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<td>-.194</td>
<td>0.22</td>
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<tr>
<td>$\Delta$ Insulin</td>
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### b)

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<th>p-value</th>
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