Impaired Postprandial Blood Flow in Adipose Tissue May Be an Early Marker of Insulin Resistance in Type 2 Diabetes

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OBJECTIVE — We investigated the changes in subcutaneous adipose tissue blood flow (ATBF) after a meal in the various stages of type 2 diabetes.

RESEARCH DESIGN AND METHODS — Five groups were examined: healthy control subjects, first-degree relatives of subjects with type 2 diabetes, subjects with impaired glucose tolerance (IGT), subjects with type 2 diabetes and postprandial hyperglycemia but normal fasting plasma glucose levels (diabetes group A [DMA]), and subjects with type 2 diabetes with both postprandial and fasting hyperglycemia (diabetes group B [DMB]). ATBF was measured with ^{133}Xe.

RESULTS — ATBF was higher in control subjects (1,507 ± 103 ml/100 cm^3 tissue × min) versus relatives and IGT, DMA, and DMB subjects (845 ± 123, 679 ± 69, 765 ± 60, and 757 ± 69 ml/100 cm^3 tissue × min, respectively; $P < 0.001$). Insulin sensitivity index (ISI) in control subjects (82 ± 3 mg × l^2/mmol × mU × min) was higher versus that for relatives and IGT, DMA, and DMB subjects (60 ± 3, 45 ± 1, 40 ± 6, and 29 ± 4 mg × l^2/mmol × mU × min, respectively; $P < 0.0001$). ISI was positively associated with peak-baseline ATBF (β coefficient 0.029 ± 0.013, $P = 0.03$).

CONCLUSIONS — After meal ingestion, insulin-stimulated ATBF was decreased in relatives and and IGT, DMA, and DMB subjects. This defect could be an early marker of insulin resistance that precedes the development of type 2 diabetes.

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Blood flow plays an important role in the metabolic function of adipose tissue and normally increases after meal ingestion (1). In insulin-resistant states such as obesity or type 2 diabetes, this response is blunted (2–4). Whether this defect, which may be another facet of the insulin resistance syndrome (5), occurs early in the development of type 2 is unknown.

Our study was undertaken to examine adipose tissue blood flow (ATBF) at all stages of type 2 diabetes. In addition, changes in plasma levels of adiponectin and apelin were also examined, since these adipokines correlate positively with endothelium-dependent vasodilatation (6–8).

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Abbreviations: ATBF, adipose tissue blood flow; IGT, impaired glucose tolerance; ISI, insulin sensitivity index; NEFA, nonesterified fatty acids.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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RESEARCH DESIGN AND METHODS

— A meal (730 kcal, 50% carbohydrate, 38% starch, 40% fat, and 10% protein, consisting of bread, cheese, tomato, cucumber, olive oil, orange juice, and apple) was given to five groups: *1*) healthy control subjects (aged 40 ± 3 years, with BMI 24 ± 1 kg/m^2; $n = 10$), *2*) relatives of subjects with type 2 diabetes (two first-degree relatives [parents and siblings] aged 41 ± 3 years, with BMI 25 ± 1 kg/m^2; $n = 11$), *3*) subjects with impaired glucose tolerance (IGT) (aged 43 ± 3 years, with BMI 26 ± 1 kg/m^2; $n = 6$), *4*) subjects with type 2 diabetes and postprandial hyperglycemia but normal fasting plasma glucose (diabetes group A [DMA]) (aged 53 ± 4 years, with BMI 25 ± 1 kg/m^2), and *5*) subjects with type 2 diabetes and both fasting and postprandial hyperglycemia (diabetes group B [DMB]) (aged 56 ± 2 years, with BMI 26 ± 1 kg/m^2; $n = 13$).

Blood samples were withdrawn from radial artery for measurements of insulin (Linco Research, St. Charles, MO), glucose (Yellow Springs Instruments, Yellow Springs, OH), triglycerides, and nonesterified fatty acids (NEFAs) (Roche Diagnostics, Penzberg, Germany), adiponectin (DRG Diagnostics, Marbourg, Germany), and apelin (Phoenix Pharmaceuticals, Phoeniz, AZ).

ATBF was measured immediately before each blood sample (9,10). Insulin sensitivity in fasting state was measured by homeostasis model assessement (11) and in postprandial state by Gutt index (insulin sensitivity index [ISI] [12]). The study was approved by a hospital ethics committee, and subjects gave informed consent.

Statistical analysis

Comparisons between groups were performed with repeated-measures ANOVA. Multiple linear regression analysis evaluated the association between ISI, triglycerides, and NEFAs with peak-baseline ATBF after correcting for potential confounders.

RESULTS

— At 120 min, plasma glucose and insulin in control subjects were

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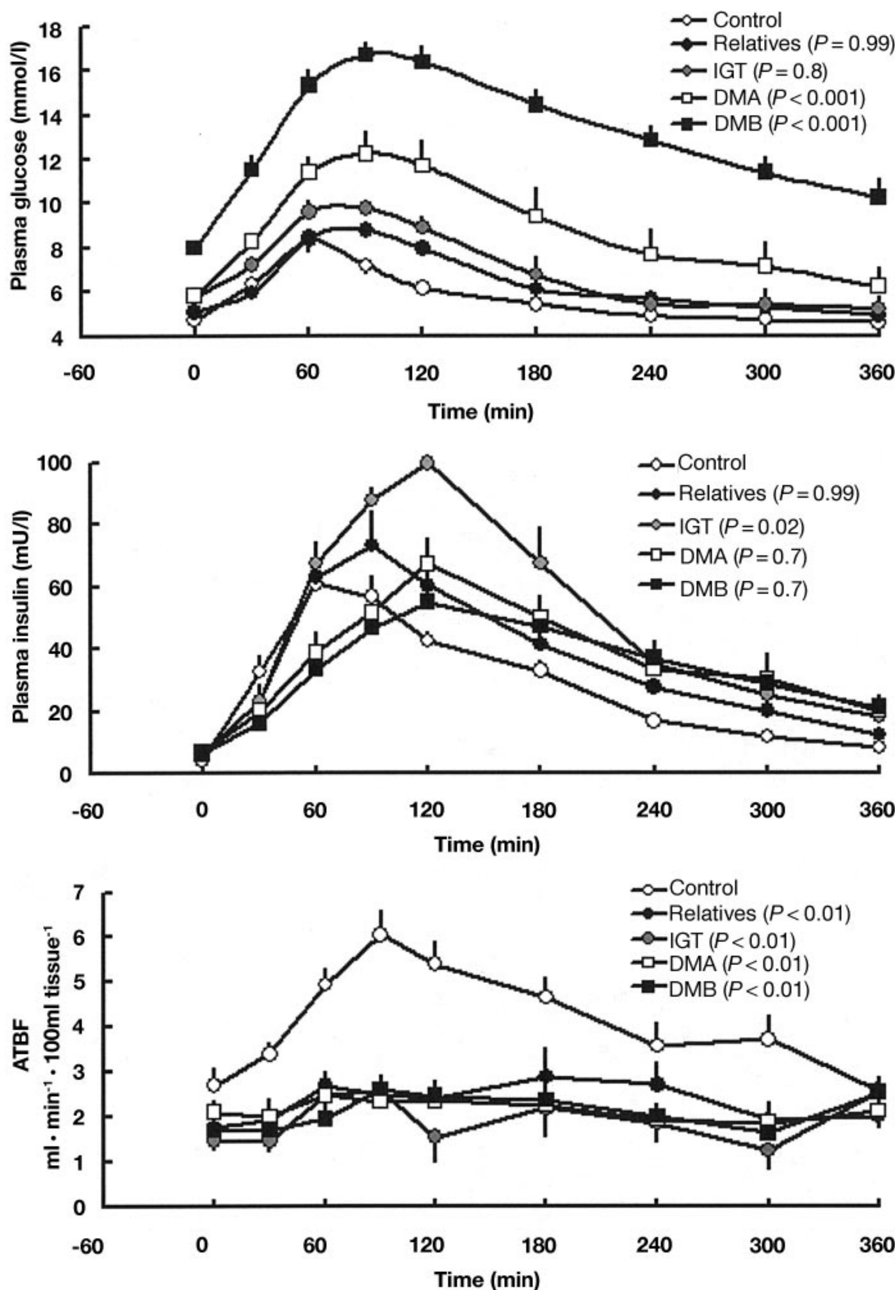

Figure 1— *Plasma glucose, plasma insulin, and adipose tissue blood flow in healthy subjects (control), first-degree relatives of subjects with type 2 diabetes (relatives), and IGT, DMA, and DMB subjects.* P *values represent overall comparison (repeated-measures ANOVA) between control and patient groups. At* t = *0, a mixed meal was given.*

lower than in relatives and IGT, DMA, and DMB subjects ($P < 0.05$) (Fig. 1). ATBF after meal ingestion was suppressed in relatives and subjects with IGT, DMA, and DMB versus control subjects ($P_{overall} < 0.001$) (Fig. 1).

Fasting triglycerides were lower in control subjects (463 ± 52 μmol/l) versus relatives and IGT, DMA, and DMB subjects (671 ± 52, 821 ± 162, 888 ± 94, and 928 ± 133 μmol/l, respectively; $P_{overall} < 0.014$). Postprandial triglycerides were lower in control subjects (264 ± 32 mmol/l × 360 min) versus relatives and IGT, DMA, and DMB subjects (336 ± 39, 505 ± 84, 470 ± 90, and 498 ± 84 mmol/l × 360 min, respectively; $P_{overall} < 0.04$). Fasting and postprandial triglycerides were negatively associated with peak-baseline ATBF (β coefficient −6.2 ± 2.8, $P = 0.03$ and −2.7 ± 1.8, $P = 0.09$, respectively).

Preprandial NEFAs were similar in control subjects (461 ± 53 μmol/l), relatives, and IGT, DMA, and DMB subjects (434 ± 44, 453 ± 129, 456 ± 50, and 714 ± 145 μmol/l, respectively; $P_{overall} = 0.218$). Postprandial NEFAs (areas under $curve_{0-360\ min}$ of the postprandial decreases) were lower in control subjects (98 ± 11 mmol/l × 360 min) versus relatives and IGT, DMA, and DMB subjects (128 ± 22, 156 ± 19, 140 ± 31, and 182 ± 16 mmol/l × 360 min, respectively; $P_{overall} < 0.02$). Fasting NEFAs were not associated with peak-baseline ATBF ($P = 0.256$); postprandial NEFAs were negatively associated with peak-baseline ATBF (β coefficient $-9.6 \times 10^{-6} \pm 0.01$; $P = 0.001$).

Homeostasis model assessment in control subjects (0.9 ± 0.1) was lower versus that in relatives and IGT, DMA, and DMB subjects (1.43 ± 0.1, 1.7 ± 0.1, 1.8 ± 0.2, and 2.2 ± 0.2, respectively; $P_{overall} = 0.003$). ISI in control subjects (82 ± 3 mg × l^2/mmol × mU × min) was higher versus that in relatives and IGT, DMA, and DMB subjects (60 ± 3, 45 ± 1, 40 ± 6, and 29 ± 4 mg × l^2/mmol × mU × min, respectively; $P_{overall} < 0.0001$). ISI was positively associated with peak-baseline ATBF (β coefficient 0.029 ± 0.013, $P = 0.03$).

Adiponectin was higher in control subjects (21 ± 3 ng/ml) and relatives (23 ± 3 ng/ml) versus IGT, DMA, and DMB subjects (11 ± 2, 13 ± 4, and 12 ± 3, respectively; $P_{overall} = 0.007$).

Apelin was similar in control subjects (1.13 ± 0.21 ng/ml), relatives, and IGT, DMA, and DMB subjects (1.02 ± 0.2, 1.51 ± 0.3, 1.5 ± 0.4, and 1.3 ± 0.3 ng/ml, respectively).

CONCLUSIONS— ATBF is blunted after meal ingestion at all stages of type 2 diabetes. Since insulin is a mediator of the postprandial increases in ATBF (13), these results suggest that suppressed ATBF may be a marker of insulin resistance. Indeed, insulin sensitivity in our subjects was positively associated with the increases in ATBF after the meal. However, it should be pointed out that this is a cross-sectional analysis; although findings of impaired ATBF in people at high risk for diabetes imply that this abnormality might precede the development of clinical diabetes, the analysis does not actually prove this, and the suggestion remains speculative.

Our results confirm previous findings in obese (2,3) or lean (4) subjects with overt type 2 diabetes in whom ATBF rates were decreased after the consumption of a

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mixed meal or glucose. Jansson et al. (2) showed that ATBF is lower in insulin-resistant subjects with obesity and/or type 2 diabetes and that this correlates negatively with the blood pressure.

Our results do not agree with a report (14) in first-degree relatives of diabetic subjects in whom ATBF was measured during a hyperinsulinemic-euglycemic clamp: in the presence of insulin, these rates were decreased by 46% compared with those in healthy control subjects, but the differences were not significant. The differences with our study can be explained by the findings of Karpe et al. (13): *1*) the increases in ATBF after oral administration of glucose were significantly greater than those after intravenous infusion of insulin, and 2) locally infused insulin at the abdominal subcutaneous adipose tissue had no demonstrable effects on blood flow, suggesting that insulin does not have a direct effect on ATBF but, rather, is a mediator acting via sympathetic activation.

The physiological significance of the nutrient-related decreases in ATBF in the patient groups of our study is unclear. However, changes in postprandial plasma triglyceride and NEFA responses were negatively associated with ATBF. These results agree with the study of Samra et al. (15), in which triglyceride clearance by adipose tissue was closely related to ATBF when increased by epinephrine infusion. Moreover, Karpe at al (5) showed that, in healthy subjects, the postmeal ATBF response is related to insulin sensitivity; of all of the indexes of insulin sensitivity used, the estimation based on NEFA suppression to insulin was most strongly related to the ATBF response, suggesting that ATBF may be a major determinant of the insulin-related changes in plasma NEFAs after the meal.

Plasma adiponectin was decreased in the subjects with IGT and type 2 diabetes. However, it is unlikely that adiponectin may mediate the changes seen in ATBF, since in the relatives, plasma adiponectin levels were normal but ATBF decreased.

In conclusion, we have shown that ATBF is suppressed after meal ingestion at all stages of type 2 diabetes. These findings may provide a marker of insulin resistance that occurs early in the development of type 2 diabetes.

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