

# Impaired Postprandial Adipose Tissue Blood Flow Response Is Related to Aspects of Insulin Sensitivity

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Obesity has been associated with dysfunctional postprandial adipose tissue blood flow (ATBF), but it has also been recognized that the interindividual response is highly variable. The present work aimed at characterizing this variability. Fifteen subjects were given 75 g oral glucose, and abdominal subcutaneous ATBF was monitored by the <sup>133</sup>Xe washout method. Determinants of insulin sensitivity based on nonesterified fatty acid (NEFA) suppression after oral glucose administration [ISI(NEFA)] were higher in the top tertile ATBF response group ( $1.29 \pm 0.09$  vs.  $0.90 \pm 0.08$  in the lower tertiles,  $P = 0.01$ ). ISI(NEFA) was related to ATBF response ( $r_s = 0.73$ ,  $P < 0.002$ ) as well as insulin sensitivity based on postprandial glycemia [ISI(gly),  $r_s = 0.58$ ,  $P < 0.05$ ], whereas the homeostasis model assessment (HOMA) index ( $r_s = -0.39$ ,  $P = 0.16$ ) was not. The relationship between increase in ATBF and ISI(NEFA) was independent of BMI ( $P = 0.015$ ) in multivariate analysis. Subjects with a high ATBF response had significantly higher increase of plasma norepinephrine ( $P < 0.05$ ), indicating a link between postprandial insulinemia, sympathetic activation, and ATBF response. There is a close relationship between insulin sensitivity and the regulation of postprandial ATBF, independent of adiposity. Impaired regulation of ATBF seems to be another facet of the insulin resistance syndrome. *Diabetes* 51:2467–2473, 2002

It has recently become clear that the responsiveness of adipose tissue blood flow (ATBF) to nutrient ingestion is related to adiposity. ATBF in obese subjects tends to respond less to mixed meal ingestion than in lean subjects (1,2). However, obesity only explains a part of the rather high variability in postprandial regulation of ATBF seen between subjects, and other aspects have not been well studied. Because of the relationship between ATBF and triglyceride (TG) clearance, it has been proposed that impairment of nutrient-induced

blood flow responses in both skeletal muscle and adipose tissue may jointly underlie some of the deleterious aspects of insulin resistance (3).

It is increasingly recognized that impairment of endothelial and vascular function is an integral part of the insulin resistance syndrome. Indeed, it has been suggested that impairment of endothelial-dependent vasodilatation in skeletal muscle may underlie impaired glucose utilization in response to insulin (4,5), although the physiological significance of those observations has been questioned (6). Impairment of endothelial function is also closely associated with future cardiovascular events (7–9).

Although endothelial function has usually been studied in terms of nitric oxide-dependent dilatation of limb or skeletal muscle blood flow, the blood supply to other tissues is also regulated according to physiological or nutritional state. ATBF is highly variable in time, responding over a far greater range than skeletal muscle blood flow to a variety of conditions. For instance, ATBF increases in response to stress states such as exercise (10,11) or mental stress (12) and also in response to nutrient intake (1,2,13,14). The physiological significance of the nutrient-related increase in ATBF is not known, although it is interesting that TG clearance by adipose tissue is closely related to blood flow when this is increased by epinephrine infusion (15).

The factors that determine ATBF responsiveness to nutrients have not been clearly defined. It is not known whether the primary determinant of responsiveness is obesity per se or the associated insulin resistance. In this work, we set out to test the hypothesis that ATBF responsiveness to nutrients is related primarily to aspects of insulin sensitivity. We first compared the ATBF response to oral glucose ingestion and intravenous glucose/insulin infusions, primarily to verify reproducibility of ATBF responsiveness within a group of apparently healthy subjects. Secondly, we examined the factors affecting the variability of the ATBF response. To more specifically target adipose tissue insulin sensitivity, we used novel insulin sensitivity indexes based on nonesterified fatty acid (NEFA) suppression (16) and postprandial glucose and insulin concentrations (16,17). Mechanisms of the potential regulation of ATBF by insulin have previously been reported in this group of subjects (18).

## RESEARCH DESIGN AND METHODS

**Oral versus intravenous glucose administration.** For the main study, 15 healthy subjects (10 men and 5 women) participated; their median age was 32 years (range 23–52), and their median BMI was 23.6 kg/m<sup>2</sup> (range 19.4–29.6).

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ATBF, adipose tissue blood flow; HOMA, homeostasis model assessment; ISI(gly), insulin sensitivity based on postprandial glycemia; ISI(NEFA), insulin sensitivity based on NEFA suppression after oral glucose administration; NEFA, nonesterified fatty acid; RM-ANOVA, repeated-measures ANOVA; TG, triglyceride.

They were studied at rest, following an overnight fast, and asked to refrain from strenuous exercise, smoking, or alcohol for 24 h beforehand. They attended on two occasions, 2–4 weeks apart; on the first, 75 g oral glucose was given, and on the second, similar plasma concentrations of insulin and glucose were achieved by dynamic intravenous infusions (intravenous insulin/glucose).

A cannula was inserted retrogradely into a distal forearm vein and kept patent by a continuous slow infusion of saline (NaCl 9 g/l). The lower part of the forearm was heated to provide arterialized blood samples. Samples were taken at 10-min intervals throughout the study into heparinized tubes. At  $t = 0$ , 75 g glucose, dissolved in 200 ml water and flavored with fresh lemon, was ingested. Plasma glucose was measured the same day on samples stored at 4°C using an enzymatic method. Plasma insulin was measured by radioimmunoassay (Pharmacia and Upjohn, Milton Keynes, U.K.). Plasma NEFAs were measured using the Wako NEFA C kit (Alpha Laboratories, Eastleigh, U.K.) and TGs were measured by an enzymatic micromethod (19). These analyses were performed on samples stored at –20°C. Plasma norepinephrine was measured by high-performance liquid chromatography with electrochemical detection (20) on samples stored at –70°C. Metabolic data are given in full elsewhere (18) and are only reported in summary form here.

ATBF was measured by the  $^{133}\text{Xe}$  washout technique (21). A dose of 2 MBq of  $^{133}\text{Xe}$  in 0.9% saline was injected into the para-umbilical area of the subcutaneous adipose tissue, ~10 mm deep. After an equilibration period of 30 min, ATBF was monitored by collecting continuous 20-s readings from a  $\gamma$ -counter probe placed over the exact site of injection and taped firmly in place (14). Blood flow was calculated from a semilog plot of disappearance of counts versus time in 10-min intervals. ATBF was then calculated according to the equation  $\text{ATBF} = \text{slope of semilog plot} \times \text{partition coefficient} \times 100$  (14,21). The partition coefficient was taken as 10 g/ml for these nonobese subjects.

The second visit involved intravenous administration of glucose (200 mg/ml) and insulin (10 units of insulin in 58 ml of saline + 2 ml of homologous blood) to achieve plasma glucose and insulin concentrations mimicking the first study. Insulin infusion was modified from algorithms developed by Kearney et al. (22). The initial insulin infusion rate was  $0.6 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  from time 0 to +30. The following infusion rates were 0.4 (30–45 min), 0.3 (45–60 min), 0.2 (60–90 min), and 0.1  $\text{mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  (90–150 min), respectively. Glucose infusion was varied to match the pattern after oral ingestion of glucose, and blood glucose concentration was monitored every 5 min to adjust the glucose infusion rate using a reflectometer (Hemocue).

**Second independent dataset.** Because some of the more important findings from the main study were in the nature of associations, we sought to examine these in an independent dataset. For this purpose, we reanalyzed data from 15 healthy nonobese subjects (2 men, median age 43 years, range 18–70, median BMI 24.6  $\text{kg}/\text{m}^2$ , range 19.5–30.0) studied previously in investigations of the effects of dietary TG structure on metabolism (23,24). Each person was studied on two occasions after overnight fast. The order of experiments was randomized, and for these purposes, we have arbitrarily taken “visit 1” to be the occasion on which they ingested TGs in the form SUU (where S = saturated, U = unsaturated). ATBF was measured as described above. After baseline measurements and blood samples, the subjects were given a mixed meal containing 85 g carbohydrate, 60 g fat, and 30 g protein; only the structure of the TG comprising most of the fat differed between studies. ATBF measurements were made, and blood samples taken, for 6 h after the meal. Analytical methods were as for the main group.

**Calculations and statistics.** Calculations were done with SPSS for Windows Release 9.0 (SPSS, Chicago). Changes in concentrations with time were assessed by repeated-measures analysis of variance (RM-ANOVA) using time and treatment as within-subjects factors.

Peak values for ATBF were calculated as the greatest running mean of three adjacent points between 0 and 100 min; time-to-peak ATBF was taken as the time of the midpoint of these three values. Absolute change in ATBF (or ATBF response) was calculated as peak minus mean baseline.

Insulin sensitivity indexes for glycemia [ISI(gly)] and NEFA suppression [ISI(NEFA)] were calculated as follows:

$$\text{ISI}(\text{gly}) = 2/[(\text{INSp} \times \text{GLYp}) + 1]$$

$$\text{ISI}(\text{NEFA}) = 2/[(\text{INSp} \times \text{NEFAp}) + 1]$$

where INSp, GLYp, and NEFAp are insulin, glucose, and NEFA area under the curve, respectively, over 2 h after glucose ingestion, expressed relative to average values from the group of subjects (16). Insulin sensitivity was also calculated using a minimal model index [ $S_{1(\text{oral})}$ ], from plasma glucose and insulin concentrations after oral glucose (17) and from fasting glucose and insulin concentrations using homeostasis model assessment (HOMA) (25).

Data from the subsidiary group were analyzed in two ways. For examination of the reproducibility of ATBF response, the data from the two visits were compared. For further analysis, data for each subject were averaged over the

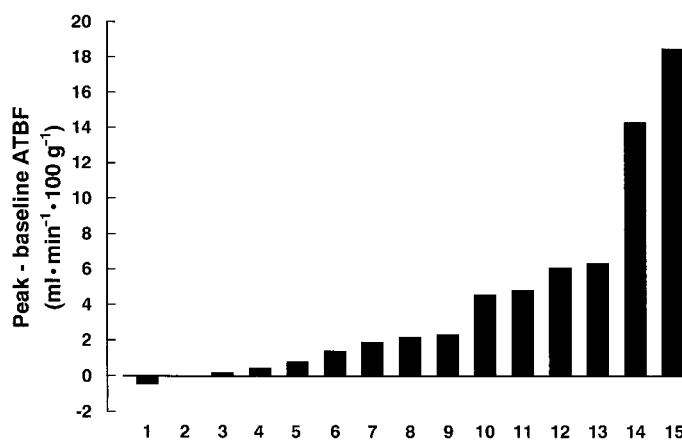


FIG. 1. ATBF response to oral glucose ingestion in 15 subjects. Bars represent ATBF response defined as peak value minus baseline. The response was significantly different between subjects ( $P < 0.001$ ).

two visits. Although ISI(gly) and ISI(NEFA) were not intended to be used with mixed meals (16), we calculated them in exactly the same way over the first 2 h. The minimal model index  $S_{1(\text{oral})}$  described above (17) was calculated over the 6 h postprandial period. Peak ATBF and ATBF response were calculated as described for the main group.

Averages are expressed as means  $\pm$  SE of the mean (SE) or median and range. Differences between subjects were assessed by the Mann-Whitney  $U$  test. The Spearman correlation coefficient ( $r_s$ ) was used to test for associations between variables. In multivariate stepwise regression analysis, the included parameters were log transformed.

The Central Oxford Research Ethics Committee approved the studies, and all subjects gave informed consent after the procedure had been fully explained.

## RESULTS

**Heterogeneity of ATBF responses to oral and intravenous glucose.** Although ATBF increased on average in response to oral glucose, there was marked heterogeneity in response between subjects (Fig. 1,  $P < 0.001$ ). Of 15 subjects, 9 exhibited an increase in ATBF (peak-baseline) in response to oral glucose  $>50\%$ ; the range for all subjects was  $-8.5$  to  $405\%$ . The median increase was  $94.3\%$ . Similarly, there was heterogeneity of ATBF response to intravenous glucose/insulin ( $P < 0.001$ ). Of the 15 subjects, 6 exhibited an increase in ATBF in response to intravenous glucose/insulin that was  $>50\%$ ; the range for all subjects was  $-37.4$  to  $247\%$ .

For both regimens, peak ATBF was significantly correlated with baseline ATBF ( $r_s = 0.60$ ,  $P < 0.05$  and  $r_s = 0.72$ ,  $P < 0.05$  after oral and intravenous glucose, respectively). There was a significant correlation between peak ATBF after oral and intravenous glucose ( $r_s = 0.87$ ,  $P < 0.001$ ), and the increase in ATBF was significantly correlated between the two treatments ( $r_s = 0.55$ ,  $P < 0.05$ ), showing that subjects can be reliably characterized as “responders” or “nonresponders.”

Given the marked heterogeneity in ATBF response between subjects, and that some subjects showed an increase in blood flow on both days, whereas several showed no response to either oral glucose or intravenous glucose/insulin, the subjects were divided into tertiles according to the magnitude of the increase in ATBF after oral glucose (Fig. 2). This created three groups with distinctly different blood flow responses: mean values ( $\pm$ SE) for the increase in blood flow were  $0.18 \pm 0.20$ ,  $2.45 \pm 0.55$ , and  $9.98 \pm 2.71 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$  for low, medium, and high responder groups, respectively. In the high tertile, the mean increase

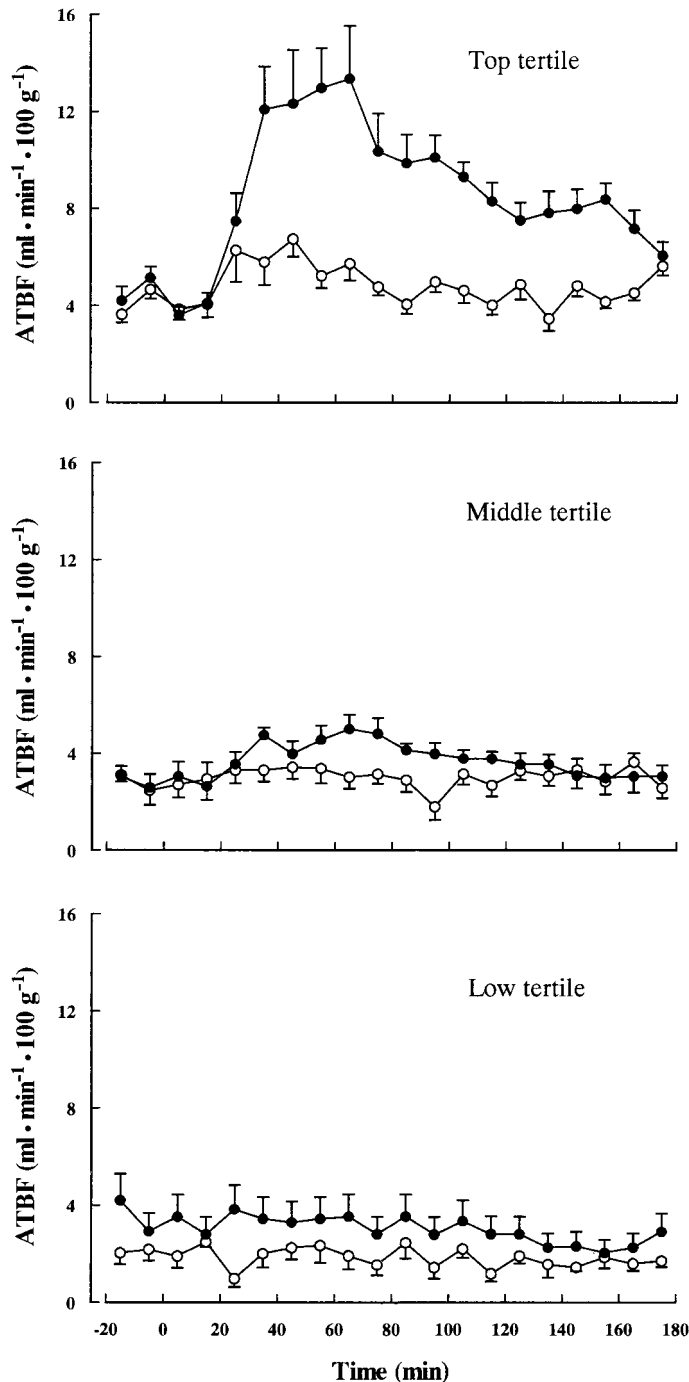


FIG. 2. Tertiles of ATBF response to oral glucose (●) and intravenous glucose/insulin (○) in 15 subjects. Tertiles were defined by peak value minus baseline in response to oral glucose. Results are expressed as means  $\pm$  SE. There was a significant ATBF increment for the top ( $P < 0.05$ ) and middle ( $P < 0.05$ ) tertiles.

was  $212 \pm 49\%$ . The medium and low tertiles were  $117 \pm 35$  and  $8.2 \pm 6.9\%$ , respectively. Despite very close modeling of the postprandial glucose and insulin concentrations (18), the ATBF response to intravenous insulin/glucose was lower than that to oral ingestion of glucose (Fig. 2). However, the relative response within subjects seemed to be reproducible with mean increases of  $0.33 \pm 0.45$ ,  $0.93 \pm 0.31$ , and  $3.27 \pm 1.41 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$  for low, medium, and high responder groups, respectively. In addition, if the subjects were ranked according to the

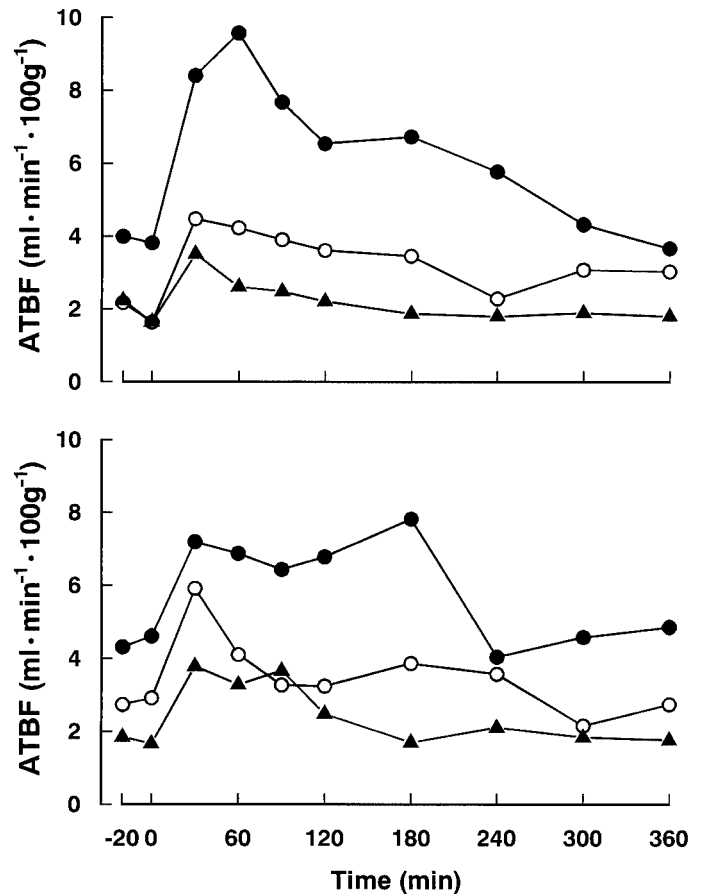


FIG. 3. ATBF responses to mixed meal ingestion in 15 normal subjects on two occasions. Top panel: data for first visit, divided into tertiles of ATBF response. Lower panel: data for second visit, divided into tertiles of ATBF response (peak minus baseline) on the first visit. ●, top tertile ( $n = 5$ ) of ATBF response on first visit; ○, middle tertile of ATBF response on first visit; ▲, lowest tertile of ATBF response on first visit.

magnitude of ATBF increase after intravenous glucose/insulin instead of after oral glucose, the mean response in each tertile was almost identical. This indicates that the ATBF response is inherent within a subject, irrespective of the origin of the stimulus.

The independent dataset of 15 subjects who received a mixed meal on two occasions was also used to assess reproducibility of the ATBF response to nutrient ingestion. The pattern of blood flow response was similar to that seen after oral glucose, although more prolonged. As seen with oral glucose, subjects differed in their degree of response and were divided into tertiles of absolute ATBF response on their first visit (Fig. 3). When their ATBF responses on the second visit were plotted in the same way, ranked by response on the first visit, it was clear that the group of highest responders remained consistent responders, and the other subjects remained consistently low responders (Fig. 3). The peak ATBF values were correlated between the two visits ( $r_s = 0.73$ ,  $P = 0.002$ ). **Relationships between indexes of insulin sensitivity.** The methods used for insulin sensitivity estimations showed signs of strong interdependence as well as some clear differences. This indicates that they point toward different aspects of insulin sensitivity. For example the ISI(NEFA) was strongly correlated with HOMA ( $r_s = -0.76$ ,  $P = 0.001$ ), whereas it was not significantly corre-

TABLE 1  
Characteristics of subjects divided into tertiles according to increase in ATBF after oral glucose

	Lower two tertiles ( <i>n</i> = 10)	Top tertile ( <i>n</i> = 5)	<i>P</i> (Mann-Whitney <i>U</i> )
BMI (kg/m <sup>2</sup> )	25.0 ± 0.67	21.5 ± 0.96	0.01
Insulin (pmol/l)	42.6 ± 4.4	28.14 ± 1.62	0.066
Glucose (mmol/l)	5.25 ± 0.14	4.96 ± 0.17	0.33
NEFA (μmol/l)	450 ± 59	367 ± 48	0.54
TG (mmol/l)	0.83 (0.46–4.82)	0.62 (0.46–1.16)	0.33
Total cholesterol (mmol/l)	4.67 ± 0.09	4.95 ± 0.44	0.71
<i>S</i> <sub>i (oral)</sub> (dl · kg <sup>-1</sup> · min <sup>-1</sup> per μU · ml <sup>-1</sup> ) × 10 <sup>4*</sup>	14.9 ± 2.3	22.2 ± 5.4	0.14
ISI(gly)†	0.96 ± 0.06	1.16 ± 0.06	0.09
ISI(NEFA)‡	0.90 ± 0.08	1.29 ± 0.09	0.014
HOMA§	9.12 ± 0.99	6.58 ± 0.47	0.18
Baseline ATBF (ml · min <sup>-1</sup> · 100 g <sup>-1</sup> )	2.82 ± 0.43	4.41 ± 0.42	0.037
Peak ATBF (ml · min <sup>-1</sup> · 100 g <sup>-1</sup> )	4.50 ± 0.52	14.7 ± 3.2	0.002
Peak-baseline (ml · min <sup>-1</sup> · 100 g <sup>-1</sup> )	1.31 ± 0.47	9.98 ± 2.71	0.002
Peak/baseline	1.63 ± 0.25	3.12 ± 0.49	0.014
ATBF time-to-peak (min)	59 ± 6	55 ± 7	0.62

Data are means ± SD. Plasma TG concentration expressed as median (range). Insulin sensitivity was calculated as follows: \*from a minimal model index after oral glucose (17); †from glucose area under the curve after oral glucose (16); ‡from NEFA area under the curve after oral glucose (16); §according to the homeostatic model (25).

lated with the postglucose *S*<sub>i (oral)</sub> (*r*<sub>s</sub> = 0.41, *P* = 0.13). The independent measurements of insulin sensitivity based on postmeal glucose measurement, ISI(gly), and *S*<sub>i (oral)</sub>, were significantly correlated (*r*<sub>s</sub> = 0.85, *P* < 0.001).

**ATBF response and its relationship to insulin sensitivity.** Because the subjects in the top tertile of ATBF response to oral glucose clearly showed a much more marked response than the lower two tertiles, a comparison was made between these subjects and the low and middle tertiles combined (Table 1). By definition, the increase in ATBF was significantly different in the top tertile, but other indexes of ATBF, i.e., baseline ATBF, peak ATBF, and peak/baseline ATBF, were also significantly higher. Subjects in the top tertile had significantly greater values for some measures of insulin sensitivity, as well as lower BMI, than the low and middle responders. Therefore, associations between metabolic and anthropometric variables and response of ATBF were sought.

As expected, BMI was significantly correlated with the indexes of insulin sensitivity, being negatively associated with ISI(NEFA) (*r*<sub>s</sub> = -0.62, *P* = 0.01), ISI(gly) (*r*<sub>s</sub> = -0.59, *P* = 0.02), and *S*<sub>i (oral)</sub> (*r*<sub>s</sub> = -0.55, *P* = 0.03) and positively associated with HOMA (*r*<sub>s</sub> = 0.63, *P* = 0.01). However, the increase in ATBF showed a varying degree of association with these indexes as follows. Increase in ATBF was negatively correlated with BMI (*r*<sub>s</sub> = -0.57, *P* < 0.05) and was also significantly correlated with ISI(NEFA) (*r*<sub>s</sub> = 0.73, *P* < 0.002) (Fig. 4) and ISI(gly) (*r*<sub>s</sub> = 0.58, *P* < 0.05), but not with *S*<sub>i (oral)</sub> (*r*<sub>s</sub> = 0.42, *P* = 0.12) or HOMA (*r*<sub>s</sub> = -0.39, *P* = 0.16). Due to the interdependence of ATBF, BMI, and ISI(NEFA), a multivariate stepwise regression analysis was performed. The relationship between increase in ATBF and ISI(NEFA) was independent of BMI (*P* = 0.015).

The increase of the plasma concentration of norepinephrine was quantified as a surrogate marker of sympathetic activation. These data have previously been used to show that there is a positive correlation between the increase in postmeal norepinephrine and the magnitude of increase in ATBF. Here, we dichotomized the subjects according to high or low/absent increase in ATBF and

plotted the change in norepinephrine concentration for the two groups (Fig. 5). All subjects with a high ATBF increase exhibited elevation of plasma norepinephrine, whereas the nonresponders were randomly distributed around zero.

The peak insulin concentration after oral glucose intake was normally seen at, or close to, 60 min. The increase in insulin (60 min – baseline) was negatively correlated with the increase in ATBF (peak – baseline) (*r*<sub>s</sub> = -0.764, *P* = 0.001). None of the subjects in the top-tertile ATBF response group had an increase in insulin >50 pmol/l. Again, this suggests that ATBF response is intimately related to insulin sensitivity, as the people with the smallest insulin response to a given amount of oral glucose had the highest ATBF response.

**Confirmation in the independent data set.** We sought to confirm these relationships in the additional group of 15 subjects who were given a mixed meal of the same macronutrient composition on two occasions. The data from each individual's two visits were averaged. Subjects were divided into tertiles of ATBF response and again,

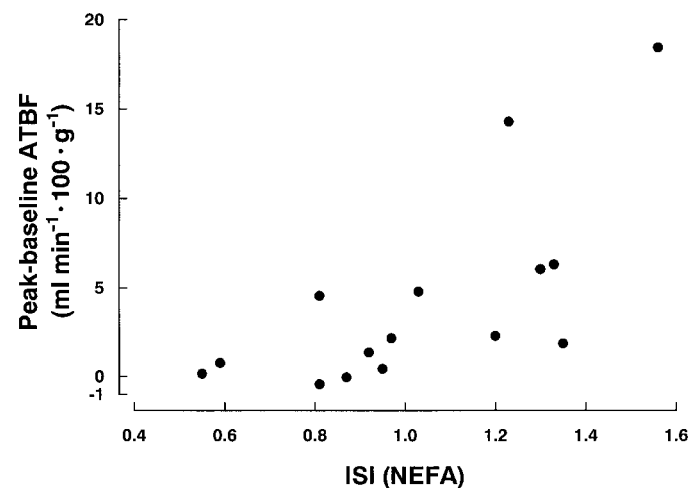


FIG. 4. Relationship between ATBF response to oral glucose ingestion and ISI(NEFA) in 15 healthy subjects. The relationship is significant (*r*<sub>s</sub> = 0.73, *P* < 0.002).

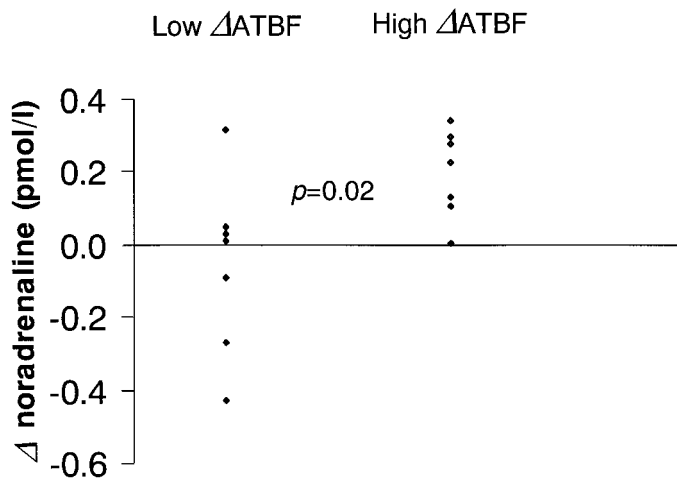


FIG. 5. Change in plasma norepinephrine concentration in 14 samples taken after either oral glucose or intravenous glucose/insulin, as described in the study by Karpe et al. (18), dichotomized according to the ATBF response. The groups were compared with the Mann-Whitney *U* test.

because the lower two tertiles showed distinctly less response than the top tertile, we compared the lower two-thirds with the top tertile (Table 2). Measures of insulin sensitivity distinguished the responders and non-responders better than BMI.

#### DISCUSSION

We have shown that subcutaneous ATBF is very responsive to nutrient ingestion, but that the response is variable between apparently healthy people. In agreement with a previous work (2), we have found that postprandial ATBF is a reproducible trait within subjects. Furthermore, when comparing ATBF after oral glucose or intravenous glucose/insulin, the ATBF response seemed to be inherent within a subject, irrespective of the origin of the stimulus. We have previously shown that the postprandial ATBF response is attenuated in obesity (1,2), and the present study identifies that the underlying mechanism is related to insulin sensitivity. In fact, here we show that the postmeal ATBF response is related to insulin sensitivity

independently of BMI. We used several indexes of insulin sensitivity, and the estimation based on NEFA suppression to insulin was most strongly related to the ATBF response. Although this indicator of insulin sensitivity shows a good correlation with whole-body insulin sensitivity, we believe that it might specifically target the insulin sensitivity of adipose tissue. Therefore, in addition to antilipolysis, blood flow regulation of adipose tissue is also likely to be related to insulin action in the tissue.

We have recently shown that the ATBF response to insulin is unrelated to the insulin concentration in the tissue by showing that local delivery of insulin to adipose tissue does not change ATBF (18). It can therefore be speculated that hyperinsulinemia affects ATBF indirectly by the well-known activation of sympathetic activity (26,27). We used the postmeal increase of norepinephrine as an indicator of sympathetic activation, and the present study shows that plasma concentrations of norepinephrine were related to an augmented response of postmeal ATBF. It has also been shown that obese, i.e., insulin-resistant subjects, have an increased muscle sympathetic activity in the fasting state and that the response to elevation of insulin in plasma gives a blunted response in terms of sympathetic activation (28). Accordingly, there may be several levels at which the degree of insulin resistance could interfere with the physiological regulation of postmeal ATBF. First, the reception of the insulin signal in the hypothalamus could be desensitized, indicated by the impaired muscle sympathetic nerve activity in response to hyperinsulinemia in obese people. Second, longstanding hyperinsulinemia may give rise to a desensitization to the increased sympathetic outflow in the target tissue, i.e., downregulation of  $\beta$ -adrenoreceptors in the vascular bed of adipose tissue. We hypothesize that these two mechanisms, possibly in combination, provide the basis for the enormous variability of postmeal ATBF response observed in this and other studies.

Until now, we have discussed the importance of insulin sensitivity in regulating a physiological postmeal ATBF response, but could it be that the ATBF response is also a determinant of whole-body insulin sensitivity? Two lines

TABLE 2

Characteristics of subjects divided into tertiles according to increase in ATBF after a mixed meal

	Lower two tertiles ( <i>n</i> = 10)	Top tertile ( <i>n</i> = 5)	<i>P</i> (Mann-Whitney <i>U</i> )
BMI (kg/m <sup>2</sup> )	25.2 ± 1.0	22.8 ± 1.1	0.18
Insulin (pmol/l)	34.5 ± 5.2	30.6 ± 3.5	0.90
Glucose (mmol/l)	5.12 ± 0.16	4.80 ± 0.10	0.18
NEFA (μmol/l)	805 ± 40	568 ± 70	0.020
TG (mmol/l)	0.99 (0.64–4.01)	0.83 (0.55–2.04)	0.33
Total cholesterol (mmol/l)	5.35 ± 0.44	4.32 ± 0.44	0.027
<i>S</i> <sub>i (oral)</sub> (dl · kg <sup>-1</sup> · min <sup>-1</sup> per μU · ml <sup>-1</sup> ) × 10 <sup>4*</sup>	18.4 ± 3.9	54.0 ± 19.9	0.086
ISI(gly)†	1.15 ± 0.06	1.50 ± 0.11	0.020
ISI(NEFA)‡	1.23 ± 0.05	1.51 ± 0.09	0.027
HOMA§	8.0 ± 1.35	6.54 ± 0.77	0.81
Baseline ATBF (ml · min <sup>-1</sup> · 100 g <sup>-1</sup> )	2.37 ± 0.38	3.52 ± 0.97	0.18
Peak ATBF (ml · min <sup>-1</sup> · 100 g <sup>-1</sup> )	4.17 ± 0.47	7.55 ± 0.90	0.005
Peak-baseline (ml · min <sup>-1</sup> · 100 g <sup>-1</sup> )	1.80 ± 0.19	4.04 ± 0.55	0.005
Peak/baseline	1.90 ± 0.14	2.52 ± 0.40	0.18
ATBF time-to-peak (min)	84 ± 12	60 ± 0	0.12

Data are means ± SE. Plasma TG concentration expressed as median (range). Insulin sensitivity was calculated as follows: \*from a minimal model index after oral glucose (17); †from glucose area under the curve after oral glucose (16); ‡from NEFA area under the curve after oral glucose (16); §according to the homeostatic model (25).

of evidence suggest that this may be the case. First, an increase in ATBF enhances triglyceride extraction across the tissue (15), and if this occurs in concert with an efficient trapping of fatty acids in the tissue, the rest of the body would be alleviated from elevated flux of fatty acids, which, at least in the muscle, would favor glucose utilization at a lower ambient insulin concentration. Second, the endocrine functions of adipose tissue may be facilitated by an increased outflow from the tissue. A recent example of a molecule that could be implicated in such a process is adiponectin. It has been suggested that adiponectin secreted from adipose tissue signals to muscle to increase fatty acid utilization through oxidation without diminishing muscle glucose uptake (29,30). Furthermore, it has also been shown that adiponectin reduces hepatic glucose production (30), which would also decrease the demands for insulin-mediated glucose turnover. However, the regulation of adiponectin secretion from human adipose tissue remains to be established, in particular in relation to blood flow.

One of the limitations of the present study is the limited number of subjects. We do however believe that the replication of the basic findings in the two independent datasets provide us with a strong argument against a type 1 error. In addition, estimation of insulin sensitivity based on postprandial responses of glucose, insulin, and NEFA have not been thoroughly evaluated, and in particular, there is a need to develop a method to determine adipose tissue insulin sensitivity. The present study aimed at investigating functional aspects of adipose tissue in relation to insulin sensitivity. Suppression of NEFA release by insulin is one of the most prominent responses in adipose tissue, and we have therefore used a novel technique to estimate adipose tissue insulin sensitivity using postprandial NEFA concentrations.

In summary, we have detected a close relationship between insulin sensitivity and the regulation of human ATBF, which is independent of adiposity. Thus, impaired regulation of postmeal ATBF is another facet of the insulin resistance syndrome, and it is speculated that the regulation of ATBF could have effects on glucose and fatty acid utilization in other tissues.

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