Whole-body and adipose tissue glucose metabolism in response to short-term fasting in lean and obese women\textsuperscript{1,3}

Jeffrey F Horowitz, Simon W Coppack, and Samuel Klein

ABSTRACT

Background: Alterations in glucose metabolism during early fasting may be an important trigger of the hormonal and metabolic responses to fasting.

Objective: The purpose of this study was to determine whether glucose metabolism in response to brief starvation differs in lean and abdominally obese women.

Design: We evaluated whole-body glucose metabolism by use of stable-isotope tracer methods and glucose uptake in subcutaneous abdominal adipose tissue by use of arteriovenous balance in 7 lean [58 ± 2 kg; body mass index (BMI; in kg/m\textsuperscript{2}): 21 ± 5] and 6 abdominally obese (96 ± 2 kg; BMI: 36 ± 1) women after 14 and 22 h of fasting.

Results: Between 14 and 22 h of fasting, whole-body glucose production and disposal declined in both groups (\(P < 0.05\)), but the reduction was 50% greater in lean than in obese women (\(P < 0.05\)). The decline in glucose uptake at 22 h of fasting was also lower in obese (0.11 ± 0.04 \(\mu\)mol·100 g\textsuperscript{-1}·min\textsuperscript{-1}) than in lean (0.26 ± 0.03 \(\mu\)mol·100 g\textsuperscript{-1}·min\textsuperscript{-1}) women (\(P < 0.05\)). Decreases in plasma insulin and leptin concentrations between 14 and 22 h of fasting were also lower in obese than in lean women (insulin: 20 ± 3\% and 32 ± 5\%; leptin: 18 ± 3\% and 37 ± 6\%; both \(P < 0.05\)).

Conclusions: The normal decline in glucose production and uptake that occurs during early fasting is blunted in women with abdominal obesity. These alterations in glucose metabolism are associated with a blunted decline in circulating concentrations of both insulin and leptin, which may explain some of the differences in the metabolic response to fasting observed between lean and abdominally obese persons. Am J Clin Nutr 2001;73:517–22.

KEY WORDS Abdominal obesity, glucose uptake, leptin, insulin, stable isotopes, women, fasting

INTRODUCTION

The early adaptive response to fasting enhances the mobilization of endogenous fat (1, 2), whereas glucose oxidation (3) and energy expenditure (4) are suppressed. These metabolic adaptations are important for survival during periods of food deprivation, resulting in the conservation of energy and preservation of glucose for use by the central nervous system. The reduction in glucose metabolism during early starvation may be a signal for initiating the neuroendocrine response to fasting by triggering a decline in plasma insulin and leptin concentrations (5). Changes in these hormones are largely responsible for regulating substrate use and energy expenditure (6, 7). Therefore, metabolic alterations during fasting are carefully integrated and may be mediated, in part, by a decline in glucose metabolism.

We found recently that many of the hormonal and metabolic responses to early starvation are altered by obesity (2, 8). The normal reductions in plasma insulin and leptin concentrations that occur during the first 24 h of fasting are blunted in women with abdominal obesity (8), which may be responsible for the blunted alterations in lipolysis and sympathetic nervous system (SNS) activity observed in obese women (2). Differences in insulin and leptin secretion during early starvation in lean and obese persons may be related to differences in glucose metabolism because glucose uptake and metabolism within the pancreas (9) and adipose tissue (10) stimulate insulin and leptin secretion, respectively. However, the effect of early fasting (≤24 h) on whole-body and adipose tissue glucose metabolism in persons with abdominal obesity is unknown.

The purpose of this study was to evaluate the effect of early fasting on whole-body and adipose tissue glucose metabolism in both lean women and women with abdominal obesity. We assessed endogenous glucose production by using stable-isotope-dilution techniques and adipose tissue glucose uptake by arteriovenous balance across abdominal adipose tissue after the subjects had fasted for 14 and 22 h. We hypothesized that the decline in glucose production, whole-body glucose uptake, and adipose tissue glucose uptake during fasting would be less in obese than in lean subjects.

\textsuperscript{1}From the Department of Internal Medicine, Washington University School of Medicine, St Louis, and St Bartholomew’s and The Royal London School of Medicine, London.

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\textsuperscript{3}Reprints not available. Address correspondence to S Klein, Washington University School of Medicine, 660 South Euclid Avenue, Box 8127, St Louis, MO 63110-1093.

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Subjects and Methods

Subjects

Seven lean women and 6 women with abdominal obesity (waist circumference: 115 ± 4 cm; waist-to-hip ratio: 0.92 ± 0.02) participated in this study (Table 1). Although the obese women were older than the lean women, all women were premenopausal. The lean and obese groups were matched for fat-free mass (FFM), which was determined by dual-energy X-ray absorptiometry (model QDR 1000/W; Hologic Inc, Waltham, MA). No subjects were taking any medications and all were considered to be in good health, with the exception of obesity, after a comprehensive medical examination that included a medical history, a physical examination, blood tests, and an electrocardiogram. Obese subjects were weight stable for 2 mo before the study, which was performed within the first 2 wk of the follicular phase of their menstrual cycle. Written, informed consent was obtained before initiation of the study, which was approved by the Institutional Review Board and the General Clinical Research Center of Washington University School of Medicine.

Experimental procedures

Subjects were admitted to the General Clinical Research Center at Washington University School of Medicine on the evening before the infusion study began. At 1800, lean subjects ingested a standard meal containing 50 kcal/kg body wt and obese subjects a standard meal containing 50 kcal/kg adjusted body wt. An adjusted, rather than actual, body weight, was used to determine the energy content of the evening meal in our obese subjects so that energy intake in relation to energy requirements would be similar in both lean and obese groups. Adjusted body weight was calculated as ideal body weight (IBW) + [(actual body weight − ideal body weight) × (0.25)] because only a small portion of excess body weight in obese subjects is composed of lean tissue. Carbohydrate, fat, and protein represented 55%, 30%, and 15%, respectively, of the total energy intake. At 2000, all subjects ingested a defined liquid-formula snack that contained 40 g carbohydrate, 6.1 g fat, and 8.8 g protein (Ensure; Ross Laboratories, Columbus, OH). After consuming this snack, all subjects fasted until completion of the study the next day.

The next morning, 20-gauge catheters were inserted into a forearm vein for isotope infusion and into a radial artery for blood sampling. A 22-gauge catheter (Hydrocathe; Viggo-Spectramed, Oxnard, CA) was placed in an abdominal vein draining abdominal subcutaneous adipose tissue (12). The catheter was positioned so that the tip was superior to the inguinal ligament as judged by surface anatomy. The abdominal catheter placement was successful in only 5 lean and 5 obese women. Therefore, all regional adipose tissue data were limited to these subjects.

At 0730 (after 11.5 h of fasting), a primed (100 μmol/kg, constant (10 μmol·kg⁻¹·min⁻¹) infusion of [6,6-H]glucose (98% atom percent excess; Cambridge Isotopes, Andover, MA) dissolved in a 0.9%-saline solution was started and continued for 2.5 h with use of a calibrated syringe pump (Harvard Apparatus, Natick, MA). An arterial blood sample was obtained before isotope infusion to determine the background tracer-to-tracee ratio (TTR). Arterial and abdominal venous samples were obtained simultaneously every 5 min (4 samples) between 0945 and 1000 (13 h and 45 min and 14 h of fasting) to determine plasma hormone concentrations, plasma substrate concentrations, and the glucose TTR. The isotope infusion was stopped after the last blood sample was obtained (eg, after 14 h of fasting) and the catheters were kept patent by infusing a 0.9%-saline solution at 25 mL/h. Subjects remained in bed for an additional 8 h and the infusion study protocol was repeated between 1530 and 1800 (after 19.5 h and 22 h of fasting).

Subcutaneous abdominal adipose tissue blood flow (ATBF) was measured by the 133Xe clearance technique (13). Between 0830 and 0845, ≈3.7 × 10¹⁰ Bq (100 μCi) 133Xe dissolved in 0.15 mL normal saline was slowly injected over 60 s into subcutaneous adipose tissue, 3 cm lateral to the umbilicus. A cesium iodide detector (Oakfield Instruments Ltd, Eynsham, United Kingdom) was placed directly over the site of injection and secured to the skin by tape. The decline in 133Xe was determined by collecting 10-s counts (14) continuously for 15 min (after 19.5 h and 22 h of fasting).

Analytic procedures

Plasma insulin (15) and leptin (16) concentrations were measured by radioimmunoassay. Plasma glucose concentrations were measured with a glucose oxidase autoanalyzer (Yellow Springs Instruments, Yellow Springs, OH). The plasma glucose TTR was determined by gas chromatography–mass spectrometry with an MSD 5971 system (Hewlett-Packard, Palo Alto, CA) with capillary column. Acetone was used to precipitate plasma proteins, and hexane was used to extract plasma lipids. The aqueous phase was dried under vacuum by using a Speed Vac evaporator (Savant Instruments Inc, Farmingdale, NY). Heptafluorobutyric anhydride was used to form a heptafluorobutyric derivative of glucose and ions were produced by electron impact ionization. The glucose TTR was determined by selectively monitoring ions at mass-to-charge ratios of 519 and 521.

Calculations

Physiologic and isotopic steady states were present during the last 15 min of isotope infusion at 14 and 22 h of fasting; therefore, Steele’s equation (17) for steady state conditions was used to calculate whole-body glucose kinetics. Subcutaneous ATBF was calculated from 133Xe clearance (13):

\[ \text{ATBF} = -k \times \lambda \times 100 \text{ (mL·100 g adipose tissue}^{-1} \cdot \text{min}^{-1}) \]

where \( k \) is the rate constant of the 133Xe monoexponential washout curve and \( \lambda \) is the adipose tissue-to-blood partition coefficient for xenon. The values for \( k \) were determined experimentally as \( (\ln y_2 - \ln y_1)/(t_2 - t_1) \), where \( y_1 \) and \( y_2 \) were the

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TABLE 1

Characteristics of the subjects

<table>
<thead>
<tr>
<th></th>
<th>Lean women ((n = 7))</th>
<th>Obese women ((n = 6))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>28 ± 2</td>
<td>38 ± 3²</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>58.3 ± 2.1</td>
<td>96.2 ± 1.6²</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.3 ± 0.5</td>
<td>36.4 ± 0.4²</td>
</tr>
<tr>
<td>Percentage body fat (%)</td>
<td>24.0 ± 1.7</td>
<td>52.3 ± 1.7²</td>
</tr>
<tr>
<td>Total fat mass (kg)</td>
<td>14.0 ± 1.2</td>
<td>50.3 ± 1.8²</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>42.0 ± 1.6</td>
<td>43.5 ± 1.8²</td>
</tr>
</tbody>
</table>

¹SEM.
²Significantly different from lean women, \( P < 0.05 \).
counting rates at times $t_1$ and $t_2$, respectively. The value for $\lambda$ was assumed to be 10 mL/g (18) for all subjects. Adipose tissue plasma flow (ATPF) was calculated by multiplying ATBF by $(1 - \text{hematocrit})$. Regional net adipose tissue glucose uptake was calculated as follows:

$$\text{Glucose uptake} = ([\text{glucose}]_a \times F_{ex}\text{glucose}) \times \text{ATPF}$$

(2)

where $[\text{glucose}]_a$ is the arterial glucose concentration and $F_{ex}\text{glucose}$ is the fractional extraction of glucose by adipose tissue. The following equation was used to calculate adipose tissue $F_{ex}$:

$$F_{ex} = ([\text{glucose}]_a \times TTR_a) - ([\text{glucose}]_a \times TTR_v)$$

(3)

where $[\text{glucose}]_a$ is the adipose tissue venous glucose concentration and TTR$_a$ and TTR$_v$ are the arterial and venous glucose TTRs, respectively. Whole-body adipose tissue glucose uptake was calculated as the product of regional net adipose tissue glucose uptake and total body fat mass.

**Statistical analysis**

A two-way analysis of variance (phenotype × time) with Tukey’s post hoc analysis was used to test the significance of differences in whole-body glucose kinetics, ATBF, adipose tissue glucose uptake, and plasma concentrations of insulin, leptin, and glucose. Student’s $t$ test for independent samples was used to test for significant differences in the relative changes in hormone concentrations and in glucose kinetics between 14 and 22 h in lean and obese subjects. A $P$ value $\leq 0.05$ was considered to be statistically significant. All data are expressed as means ± SEMs.

**RESULTS**

**Plasma hormone concentrations**

After 14 h of fasting, plasma insulin and leptin concentrations were significantly greater in obese than in lean subjects (Table 2). After 22 h of fasting, plasma insulin and leptin concentrations in both groups had declined significantly from concentrations after 14 h of fasting. However, the percentage decline was significantly greater in lean than in obese subjects (32 ± 5% and 20 ± 3% for insulin and 37 ± 6% and 18 ± 3% for leptin, respectively) and mean plasma insulin and leptin concentrations remained significantly greater in obese than in lean subjects.

**Whole-body glucose kinetics**

The rate of appearance ($R_a$) of glucose in plasma was equal to the rate of disappearance ($R_e$) of glucose from plasma after 14 and 22 h of fasting because steady state conditions were achieved. The $R_a$ of glucose after 14 h of fasting was not significantly different in lean (15.2 ± 0.6 $\mu$mol·kg FFM$^{-1}$·min$^{-1}$) and obese (16.0 ± 0.4 $\mu$mol·kg FFM$^{-1}$·min$^{-1}$) subjects. The $R_a$ and $R_e$ of glucose decreased in both groups with continued fasting to 22 h. However, both the absolute and the relative declines in the $R_a$ and $R_e$ of glucose were 50% greater in lean than in obese subjects (Figure 1). Consequently, after 22 h of fasting, the $R_a$ and $R_e$ of glucose were significantly greater in obese (14.5 ± 0.4 $\mu$mol·kg FFM$^{-1}$·min$^{-1}$) than in lean (13.0 ± 0.5 $\mu$mol·kg FFM$^{-1}$·min$^{-1}$) women.

**Plasma glucose concentrations**

The mean 14-h arterial plasma glucose concentration was the same in lean and obese subjects (Table 3). Continued fasting to 22 h resulted in arterial glucose concentrations that were significantly lower than concentrations after 14 h of fasting in both groups. The plasma glucose concentration in abdominal vein samples was always lower than that in radial artery samples, which indicates net glucose uptake by subcutaneous adipose tissue after 14 and 22 h of fasting in both lean and obese subjects.

**Adipose tissue blood flow**

ATBF and ATPF values after 14 h of fasting were significantly greater (>2 times) in lean than in obese subjects (ATBF: 4.2 ± 0.4 and 1.8 ± 0.2 mL·100 g$^{-1}$·min$^{-1}$; ATPF: 2.8 ± 0.3 and 1.3 ± 0.1 mL·100 g$^{-1}$·min$^{-1}$). ATBF and ATPF values did not change significantly between 14 and 22 h of fasting.

**Adipose tissue glucose uptake**

Data on regional glucose metabolism were obtained from 5 lean and 5 obese subjects. Abdominal adipose tissue glucose uptake

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Lean women ($n$ = 7)</th>
<th>Obese women ($n$ = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14-h fast</td>
<td>22-h fast</td>
</tr>
<tr>
<td><strong>Insulin (pmol/L)</strong></td>
<td>42.9 ± 4.6</td>
<td>26.7 ± 3.3 $^{3/2}$</td>
</tr>
<tr>
<td><strong>Leptin (nmol/L)</strong></td>
<td>0.45 ± 0.04</td>
<td>0.28 ± 0.04$^{2}$</td>
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$^{1/2}$ SEM.

$^{2}$ Significantly different from 14-h fast, $P < 0.05$.

$^{3}$ Significantly different from lean women, $P < 0.05$.

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*Significantly different from lean women, $P < 0.05$.

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**FIGURE 1.** Absolute and relative changes in the rate of appearance ($R_a$) of glucose between 14 and 22 h of fasting in lean ($n$ = 7) and obese ($n$ = 6) women. *Significantly different from lean women, $P < 0.05$. FFM, fat-free mass.
TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>Lean women (n = 5)</th>
<th>Obese women (n = 5)</th>
<th>mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14-h fast</td>
<td>22-h fast</td>
<td>14-h fast</td>
</tr>
<tr>
<td>Artery</td>
<td>4.9 ± 0.2</td>
<td>4.6 ± 0.1</td>
<td>4.9 ± 0.2</td>
</tr>
<tr>
<td>Abdominal vein</td>
<td>4.5 ± 0.1^†</td>
<td>4.3 ± 0.1</td>
<td>4.7 ± 0.2</td>
</tr>
</tbody>
</table>

^†Significantly different from 14-h fast. *Significantly different from 14-h value, P < 0.05. †Significantly different from artery, P < 0.05.

**DISCUSSION**

Fasting causes a coordinated series of metabolic adaptations that enhance survival. Restriction in carbohydrate intake and subsequent alterations in glucose metabolism may be an important signal for triggering the initial metabolic response. In fact, providing all daily energy requirements as lipid and no carbohydrate does not prevent the normal metabolic response to short-term fasting (19, 20). The results of the present study showed that the usual reductions in whole-body glucose production, whole-body glucose uptake, and adipose tissue glucose uptake during early fasting are blunted in women with abdominal obesity relative to lean women. These alterations in glucose metabolism may help explain some of the differences in the hormonal and metabolic responses to fasting observed in persons with abdominal obesity (2, 8).

Endogenous glucose production is important for providing fuel to glucose-requiring tissues during fasting. Total glucose production consists of hepatic glycogenolysis and both hepatic and renal gluconeogenesis. During early fasting, total glucose production decreases because of a marked decline in glycogenolysis without a compensatory increase in the rate of gluconeogenesis (21, 22). We are unaware of any studies that evaluated the contribution of liver glycogenolysis to total glucose production during fasting in nondiabetic obese subjects. The blunted decline in glucose production during fasting in our obese subjects may have been related to obesity-associated insulin resistance. The hepatic glycogen content is much higher in insulin-resistant obese subjects than in lean persons (23); therefore, the capacity for hepatic glycogenolysis is greater in obese than in lean persons during early starvation. In addition, gluconeogenesis is usually greater in obese than in lean subjects (23) because of higher circulating concentrations of gluconeogenic precursors, such as glycerol (2) and lactate (24). Insulin resistance in adipose tissue increases lipolysis and fatty acid delivery to the liver, which also stimulates hepatic glucose production (25). Therefore, the blunted decline in whole-body endogenous glucose production observed in our obese subjects may have been caused by both a prolonged maintenance of hepatic glycogenolysis and an accelerated rate of gluconeogenesis.

The alterations in glucose production and uptake during fasting in our obese subjects may help explain the blunted decline in plasma insulin and leptin concentrations because insulin and leptin production are regulated by pancreatic β cell and adipocyte glucose metabolism, respectively. Glucose uptake and metabolism by pancreatic β cells stimulate insulin secretion (9), whereas glucose uptake and metabolism in adipocytes stimulate leptin secretion (10). The importance of glucose metabolism in regulating hormonal secretion during fasting was shown by Boden et al (5), who found that preventing the decline in plasma glucose concentration during fasting attenuated the normal decline in plasma insulin and leptin concentrations. Glucose is also important in regulating leptin and insulin in the fed state; a high-carbohydrate diet, which enhances tissue glucose uptake and metabolism, results in a greater increase in both plasma leptin and insulin concentrations than does a high-fat diet (26). Therefore, greater glucose uptake and metabolism by pancreatic and adipose tissues in our obese than in our lean subjects may have been responsible for the differences in plasma insulin and leptin concentrations observed between the 2 groups. The differences in insulin and leptin metabolism may have important physiologic implications because changes in these hormones mediate the early adaptive response to fasting (6, 7). In fact, alterations in these 2 regulatory hormones could be responsible for the blunted increase in lipolysis and blunted decrease in sympathetic nervous system activity between 14 and 22 h of fasting observed previously in women with abdominal obesity (2). However, the results of the present study may not directly apply to men because leptin and insulin responses to energy restriction differ among the sexes (27).

Another major finding of the present study was that adipose tissue glucose uptake represents a quantitatively important route for glucose disposal in nondiabetic obese persons. Although basal adipose tissue glucose uptake per unit of fat mass was lower in obese than in lean subjects, estimated total adipose tissue glucose uptake as a percentage of whole-body glucose disposal was much greater in obese than in lean subjects. Total adipose tissue glucose uptake accounted for >20% of whole-body glucose disposal in our obese subjects compared with ~10% of whole-body glucose disposal in our lean subjects. In contrast, a
previous study found that adipose tissue glucose uptake accounted for only 10% of total glucose disposal in obese persons with type 2 diabetes (28), possibly because of greater adipose tissue insulin resistance and impaired adipose tissue glucose uptake in subjects with type 2 diabetes. Insulin enhances glucose metabolism in adipose tissue by increasing the translocation of GLUT4 transporters to the plasma membrane (29, 30) and by increasing the activity of key intracellular glycolytic enzymes. The GLUT4 messenger RNA and protein contents are 75% lower in adipocytes from obese subjects with diabetes than in adipocytes from weight-matched nondiabetic subjects and 85% lower in adipocytes from obese diabetic subjects than in adipocytes from lean subjects (30). Therefore, adipose tissue is an important site for maintaining glucose homeostasis in obese persons who do not have type 2 diabetes.

The consequence of the large amount of glucose taken up by adipose tissue in persons with abdominal obesity is unclear. Glucose delivered to adipose tissue can be used to synthesize glycogen or triacylglycerol or metabolized to form lactate or carbon dioxide. However, under normal conditions, the capacity for adipose tissue glycogen storage (31) and de novo lipogenesis (32) is limited. More commonly, glucose in adipose tissue leads to the formation of glycerol 3-phosphate (the backbone necessary for fatty acid reesterification to triglycerol) or lactate (the end product of anaerobic glucose metabolism). The importance of adipose tissue as a source of lactate depends on the amount of total body fat, the rate of adipose tissue glucose uptake, and the percentage conversion of glucose to lactate. Evidence from studies performed in isolated adipocytes indicates that the conversion of glucose to lactate is increased by fat cell size and insulin resistance (33). In fact, 50–70% of glucose taken up by fat cells obtained from obese or diabetic subjects is metabolized to lactate (34). However, the relative contribution of adipose tissue to whole-body lactate metabolism in humans is not clear because of conflicting data from in vivo studies. Results of an assessment of adipose tissue interstitial lactate concentrations with use of microdialysis probes support the notion that adipose tissue is a major site for lactate production (35, 36), whereas data from arteriovenous lactate balance measurements across subcutaneous abdominal adipose tissue suggest that the contribution of adipose tissue to whole-body lactate production is small (<5%) in both lean and obese subjects with diabetes (28). It is possible that, although diabetes is associated with a marked increase in adipocyte conversion of glucose to lactate (33), the low rate of adipose tissue glucose uptake in diabetic subjects limits the contribution of adipose tissue to total lactate production. The rate of adipose tissue glucose uptake in obese women in the present study suggests that adipose tissue may be a quantitatively important site for lactate production in nondiabetic obese persons.

In summary, the normal decline in whole-body glucose production, whole-body glucose uptake, and adipose tissue glucose uptake during early fasting is attenuated in women with abdominal obesity. The alterations in glucose metabolism may be responsible for the blunted decline in plasma insulin and leptin concentrations during fasting, which may explain some of the differences in the metabolic response to fasting observed between lean persons and those with abdominal obesity (2, 8). In addition, we found that adipose tissue is an important site for glucose disposal in obese women, accounting for >20% of whole-body glucose uptake. Therefore, glucose metabolism in adipose tissue may have a considerable effect on whole-body glucose homeostasis in obese subjects.

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