Specific Relation Between Abdominal Obesity and Early-Phase Hyperglycemia Is Modulated by Hepatic Insulin Resistance in Healthy Older Women

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OBJECTIVE — To describe the impact of abdominal obesity and hepatic insulin resistance on phase-specific glycemic responses in older women.

RESEARCH DESIGN AND METHODS — We studied 23 healthy older women (60–88 years old). Abdominal obesity was defined by an abdominal circumference ≥95 cm. Plasma glucose and insulin were measured in response to a 3-h oral glucose tolerance test. Insulin suppression of hepatic glucose production was determined using in vivo clamp techniques.

RESULTS — Despite identical prevailing insulin concentrations, glucose excursions 30 min postchallenge (but not later) were greater in women with abdominal obesity than in those without (162 ± 19 vs. 132 ± 16 mg/dl; $P < 0.01$). There was a strong correlation between hepatic glucose production suppression under low-dose insulin infusion and early-phase glucose excursions from the oral glucose tolerance test ($r = -0.83$; $P < 0.001$) in women with abdominal obesity, but not in women without ($r = 0.44$; $P < 0.11$).

CONCLUSIONS — Abdominal obesity relates specifically to early-phase hyperglycemia via hepatic insulin resistance, even in healthy older women.

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The relationship of excess abdominal adiposity to impaired glycemic control is well established. There are, however, few data describing the impact of abdominal fat on the glycemic burden over specific phases of the glucose response curve so that distinct obesity-related impairments in insulin secretion, suppression of hepatic glucose production, or impairments in peripheral insulin action can be identified.

RESEARCH DESIGN AND METHODS

— Healthy older (≥60 years; $n = 23$) women were recruited for participation in a 9-month aerobic exercise trial (1,2). Women were reported inactive, nonsmoking, free of any uncontrolled chronic disease, and not taking hormone replacement therapy, glucose-lowering, or cholesterol-lowering medication. Methods for determining peak aerobic capacity ($V_{O_{2peak}}$) have been previously described (1,2). For this report, we analyzed baseline data to determine relations among abdominal obesity and phase-specific glycemic response to an oral glucose challenge. All clinical procedures were performed in the Hospital Research Unit of the Yale Center for Clinical Investigation. Protocols were approved by the Human Investigations Committee of Yale University, and all eligible subjects gave written informed consent before participation.

Oral glucose tolerance test

A 75-g oral glucose tolerance test (OGTT) was performed according to the guidelines of the American Diabetes Association (3), with plasma glucose and insulin concentrations determined by standard procedures in the Core Laboratory of the Yale Center for Clinical Investigation. Several clinical indexes of glucose metabolism and insulin resistance were calculated from the OGTT. Total and 60-min areas under the glucose (AUC_G) and insulin (AUC_I) response curves were calculated by the trapezoidal method. To evaluate the ability of endogenous insulin secretion to suppress hepatic glucose production, we calculated the difference in glucose concentrations between baseline and 30 min (Δ glucose$_{30}$-glucose$_0$) of the OGTT. The insulinogenic index was calculated as the ratio of insulin to glucose values between 0 and 30 min [(Δ insulin$_{30}$-insulin$_0$)/(Δ glucose$_{30}$-glucose$_0$)] and used as an indicator of β-cell function (4). The composite whole-body insulin sensitivity index was calculated as [10,000/(glucose$_0$ × insulin$_0$)^2 × (mean glucose$_0$ − 120 × mean insulin$_0$ × 120)] (5). Insulin suppression of hepatic glucose production (%) was determined within 14 days of the OGTT in these same older women using [6,6-^{2}H]glucose during a low-dose euglycemic-hyperinsulinemic clamp according to methods recently described (2).

Body composition

The abdominal circumference (centimeters) was measured in triplicate at the umbilicus (6) by the same examiner. We performed a receiver operating characteristic analysis using both anthropometric and computed tomography data from one of our previous study populations (7) to determine that the abdominal circumference cut point of 95 cm demonstrated the greatest sensitivity (89%) and the lowest false-positive error (14%) relative to other

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cut points in correctly classifying older women as abdominally obese (according to a visceral fat area ≥100 cm^2) (6). Whole-body and site-specific muscle (kg) and fat mass (kg) scans were obtained using dual-energy X-ray absorptiometry.

Statistical analysis

Study variables demonstrating a statistically significant association with abdominal obesity (abdominal circumference ≥95 cm) in the simple analyses (correlation and independent *t* test) were then entered into separate multivariable ANOVA models to test their association with abdominal obesity independent of total fat and lean mass.

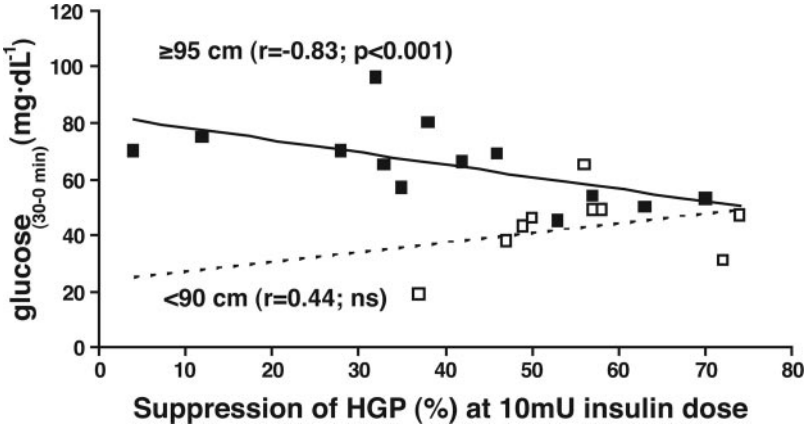

Figure 1—*Spearman rank order correlation between suppression of hepatic glucose production with low insulin infusion and 30-min change in glucose response in women with* (n = 14; ■) *and without* (n = 9; □) *abdominal obesity. Hepatic glucose production determined using in vivo tracer techniques during a two-step hyperinsulinemic-euglycemic clamp. To convert to Système International units ($\mu mol \cdot kg^{-1} \cdot min^{-1}$), multiply glucose values by 5.5. The 30-min glucose response was determined using an OGTT. HGP, hepatic glucose production.*

RESULTS — Women with (n = 14) and without (n = 9) abdominal obesity were similar with regard to age (74 ± 5 vs. 74 ± 5 years, respectively) and level of Vo_{2peak} (19 ± 4 vs. 21 ± 4 mg · kg^{-1} · min^{-1}, respectively). Total lean mass (kg) was similar between the groups (41.0 ± 6.2 vs. 37.0 ± 6.5 kg), but there was a marked difference in total body fat (30.2 ± 5.0 vs. 20.4 ± 7.2 kg) between those with and without abdominal obesity ($P < 0.001$). The mean abdominal circumference between older women characterized with abdominal obesity and those who were not was 105.7 ± 7.3 versus 81.1 ± 9.5 cm, respectively ($P < 0.001$).

In addition to significant differences in basal (99 ± 9 vs. 89 ± 8 ml/dl; $P < 0.05$) and 30-min (162 ± 19 vs. 132 ± 16 ml/dl; $P < 0.01$) glucose concentrations, the AUC_G from 0 to 60 min was significantly higher in women with abdominal obesity than in those without [89.4 ± 11.8 vs. 76.2 ± 10.2 (mg · dl^{-1} · 60 min^{-1}) · 10^2; $P < 0.01$], even though the prevailing insulin concentrations for that same time period were identical [AUC_I: 20.5 ± 10.1 vs. 20.5 ± 6.3 (μU · ml^{-1} · 60 min^{-1}) · 10^2]. When the insulinogenic index was normalized for insulin sensitivity using the whole-body insulin sensitivity index, the groups were identical in their β-cell response (insulinogenic index/whole-body insulin sensitivity index = 0.21 ± 0.19 vs. 0.21 ± 0.13 for those with and without abdominal obesity, respectively). Importantly, adjusted parameter estimates for glucose responses between 0 and 60 min were altered little by the inclusion of either total fat or lean mass in the ANOVA modeling.

To determine whether these early-phase defects in glucose response with abdominal obesity were modulated by hepatic insulin resistance, we tested the association between the change in glucose concentrations between 0 and 30 min (Δ $glucose_{30}$-$glucose_0$) of the OGTT and suppression (%) of hepatic glucose production under low-dose (10 mU) insulin stimulation. Indeed, among abdominally obese women, there was a strong inverse correlation between hepatic glucose production suppression and first-phase glucose excursions ($r = -0.83$; $P < 0.001$), which was not apparent in older women without excess abdominal fat ($r = 0.44$; $P < 0.10$) (Fig. 1).

CONCLUSIONS — We are not aware of any data linking abdominal adiposity specifically to first-phase defects in glycemic control in healthy older women. Older women with abdominal obesity demonstrated a significantly greater early (0–30 min) glucose excursion compared with their leaner counterparts. These differences in glycemic response were not observed over the later phase of the OGTT (60–180 min) and were independent of age, fitness, and total lean or fat mass. Since the prevailing insulin concentrations over the first 30 min of the OGTT were similar between the groups, insufficient insulin secretion was possibly not the primary factor in these first-phase defects in glycemic control. These findings and others (8–10) support the premise that an inability of the liver to adequately inhibit glucose production during early-phase insulin secretion is the stronger mechanism (compared with aging-related compromises in β-cell function or in peripheral insulin resistance) relating abdominal obesity to early-phase hyperglycemia in these healthy older women. We note that although we used a combination of standard clinical, highly precise imaging and in vivo procedures, the small selected sample, as well as the use of the less traditional abdominal circumference, may have compromised the generalizability of these findings to the aging population at large.

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