Specific relation between abdominal obesity and early-phase hyperglycemia is modulated by hepatic insulin resistance in healthy older women

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Running Head: Abdominal obesity and glycemic control.

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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 (60-88 y) women. Abdominal obesity was defined by an abdominal circumference ≥95 cm. Plasma glucose and insulin were measured in response to a 3-h OGTT. Insulin suppression of hepatic glucose production (HGP) was determined using in vivo clamp techniques.

Results: Despite identical prevailing insulin concentrations, glucose excursions 30-min post-challenge (but not later) were greater in women having abdominal obesity, compared with those who did not (162±19 vs. 132±16 mg·dL⁻¹; p<0.01). There was a strong correlation between HGP suppression under low-dose insulin infusion and early-phase glucose excursions from the OGTT (r=-0.83; p=0.001) in women with abdominal obesity, but not in those 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.
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 in peripheral insulin action can be identified.

**RESEARCH DESIGN AND METHODS**

Healthy older (≥60 y;n=23) women were recruited for participation in a 9-month aerobic exercise trial (1,2). Women were reported inactive, non-smoking, free of any uncontrolled chronic disease and not taking HRT, glucose- or cholesterol-lowering medication. Methods for determining peak aerobic capacity (VO_{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 Investigations (YCCI). Protocols were approved by the Human Investigations Committee of the University and all eligible subjects gave written informed consent prior to their participation.

**Oral Glucose Tolerance Test (OGTT).** A 75-g 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 YCCI. Several clinical indices 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* (IGI) 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 beta cell function (4). The *composite whole-body insulin sensitivity index* (WBISI) was calculated as (10,000/(sqrt (glucose_{0} x insulin_{0}) x (mean glucose_{0-120} x 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 [6,6-2H]glucose during a low-dose euglycemic-hyperinsulinemic clamp according to methods recently described (2).

**Body composition.** The abdominal circumference (cm) was measured in triplicate at the umbilicus (6) by the same examiner. We performed a receiver operating characteristics (ROC) 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 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 (DXA).

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

RESULTS

Women with (n=14) and without (n=9) abdominal obesity were similar with regard to age (74±5 vs. 74±5, respectively) and level of VO2peak (19±4 vs. 21±4 mg·(kg·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 vs. 81.1±9.5 cm, respectively (p<0.001).

In addition to significant differences in basal (99±9 vs 89±8 ml·dL⁻¹; p<0.05) and 30-min (162±19 vs 132±16 ml·dL⁻¹; p<0.01) glucose concentrations, the AUCG from 0-60 min was significantly higher in women with abdominal obesity compared with those without [89.4±11.8 vs. 76.2±10.2 (mg·dL⁻¹·60 min)·10²]; p<0.01], even though the prevailing insulin concentrations for that same period were identical [AUCI: 20.5±10.1 vs. 20.5±6.3 (µg·mL⁻¹·60 min)·10⁵)]. When the IGI was normalized for insulin sensitivity using the WBISI, the groups were identical in their β-cell response (IGI/WBISI=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 very 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(30-0)) of the OGTT and suppression (%) of HGP under low-dose (10 mU) insulin stimulation. Indeed, among abdominally-obese women, there was a strong inverse correlation between HGP 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)(Figure 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 to 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 to 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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Figure Legends
Figure 1 – Spearman Rank Order correlation between suppression of HGP with low insulin infusion and 30-min change in glucose response in women with (n=14; solid squares) and without (n=9; open squares) abdominal obesity. HGP=hepatic glucose production determined using in vivo tracer techniques during a 2-step hyperinsulinemic-euglycemic clamp. To convert to Systeme International units (µmol/kg·min⁻¹), multiply glucose values by 5.5. The 30-min glucose response was determined using an oral glucose tolerance test.
REFERENCES
Figure 1 –

≥95 cm ($r=-0.83$; $p<0.001$)

<90 cm ($r=0.44$; ns)

Suppression of HGP (%) at 10mU insulin dose

Glucose$_{(30-0\text{ min})}$ (mg·dL$^{-1}$) vs. Suppression of HGP (%) at 10mU insulin dose.