Role of intrahepatic lipid, central adiposity and IMCL on the insulin resistance in obese postmenopausal women

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Introduction

The prevalence of impaired glucose tolerance and type 2 diabetes increases with age and obesity. Intrahepatic lipid, central adiposity (subcutaneous and/or visceral fat) and intramyocellular lipid (IMCL) have been related to reduced insulin action (3-6). Hwang et al (7) reported the relation of intrahepatic lipid, IMCL and visceral fat to insulin sensitivity. A strong correlation between intrahepatic lipid and glucose disposal was observed in young, non-obese subjects. To our knowledge no report has been presented of the relationship between liver, abdominal and skeletal muscle fat depots to insulin resistance in obese postmenopausal women at increased risk of type 2 diabetes. Thus, the aims of the present study were twofold: 1) to analyze the relationships between hepatic lipid, central adiposity (subcutaneous and visceral fat) and IMCL all measured using ^{1}H-magnetic resonance spectroscopy and imaging in postmenopausal obese women, and 2) to examine fat depots correlations with insulin resistance.

Methods

Subjects: Eight obese normoglucose tolerant postmenopausal women (BMI: 32.8±2.1, range: 30.5~36.4. Age: 52.0±5.6, range: 44~62 yr) were studied.

MR: IMCL of right calf muscles in soleus (S); tibialis posterior (TP) and tibialis anterior (TA) were measured by ^{1}H-MR spectroscopic imaging (MRSI) (TR/TE=1000/24 ms) in a 4T Varian Inova whole body MR system with a TEM ^{1}H resonator. In-plane phase encoding (32x32) over 16.0-x16.0 cm^2 with a 10-mm slice thickness resulted in nominal voxel resolution of 0.25 ml. For internal reference purposes, water SI (TR/TE=5000/24 ms) on the same slice was also acquired with 16x16 phase encoding. For each muscle group (S, TP and TA), all 32x32 MRSI spectra were inspected and the best resolved 3-4 voxels per muscle were selected and processed. Intrahepatic lipid (IHL) content was obtained on a 1.5 T GE Signa scanner using water suppressed ^{1}H MRS via a single voxel PRESS (TR/TE=4000/28 ms) with a GE body coil. Typical voxel size was ~30 ml. Subcutaneous and visceral fat in the region from 6 cm above to 12 cm down of L2/L3 point (in three 6 cm slabs) were assessed from T1-weighted axial images (TR/TE=400/14 ms) obtained on a 1.5 T GE Signa scanner using the body coil.

Evaluation of insulin sensitivity: 3 Step (basal, 8, 40 mu/m^2/min) Hyperinsulinmic-Euglycemic pancreatic clamp with 6,6-d2 glucose tracers for measurement of insulin sensitivity within 48-hour of MR measurements.

Results and Discussion

IMCL (S, TP and TA), intrahepatic lipid (IHL), subcutaneous and visceral fat content are presented in Table 1 along with glucose disposal (Rd), basal plasma free fatty acid (FFA) and basal plasma free triglyceride (f-TG) levels. Positive correlations were observed between IHL and IMCL-S (R=0.716, p=0.046), IMCL-TA (R=0.706, p=0.050), visceral fat (R=0.772, p=0.025) and basal FFA (R=0.823,p=0.023). However, no correlation was observed between subcutaneous fat and IHL. It has been reported that the relative amount of FFAs derived from lipolysis of subcutaneous fat is quantitatively much greater than that derived from visceral fat (8). The fact that in our study the intermediate clamp step FFA positively correlated with the ratio of visceral fat to subcutaneous fat (R=0.750, p=0.032), but negatively with subcutaneous fat (R=-0.722, p=0.043) may imply that subcutaneous fat is acting more as a site for fat storage than for net lipolysis and release of FFA. The correlation of liver fat, IMCL, and abdominal fat with insulin resistance was then examined. IMCL-S showed a strong negative correlation with Rd (R=-0.902, p=0.005) while there was a modest negative correlation between Rd and IHL (R=-0.741, p=0.056). Neither subcutaneous fat nor visceral fat were correlated with Rd for this limited sized group of obese postmenopausal women.

Table 1

N=8	IMCL-S (mmol/kg)	IMCL –TP (mmol/kg)	IMCL-TA (mmol/kg)	IHL (mmol/kg)	Sub. Fat (kg)	Vis. Fat (kg)	FFA (mM)	f-TG (mM)	Rd (mg/kg-min)
Mean ± SD	8.5±2.6	6.8±3.6	2.3±1.6	142.3±137.5	4.68±1.34	1.5±0.7	0.7±0.2	0.9±0.4	4.62±1.82*

*n=7

In conclusion, non-suppression of FFA predicted IHL and visceral fat content, and negatively with subcutaneous fat consistent with the concept that excessive lipolysis drives accumulation of IHL and visceral fat and not the other way around. Excessive lipolysis may in turn drive accumulation of IHL and IMCL leading to hepatic and peripheral insulin resistance.

References

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