Simultaneous measurement of intrahepatic, intramyocellular and visceral fat content by in vivo magnetic resonance methods: Relation to insulin sensitivity

J-H. Hwang[1,2], M. Hawkins[2], D. T. Stein[2], N. Barzilai[2], J. Tonelli[2]

[1]Gruss MRRC, Albert Einstein College of Medicine, Bronx, NY, United States, [2]Medicine, Albert Einstein College of Medicine, Bronx, NY, United States

Introduction

Decreased insulin sensitivity is known to be a strong predictor for the development of type 2 diabetes (T2DM). Recent studies have indicated that intramyocellular lipid (IMCL), intrahepatic triglyceride (IHTG) and visceral fat (VF) content are all inversely correlated with insulin sensitivity [1-5]. The adipocyte-derived hormone leptin may impact insulin action via its effects on tissue triglyceride accumulation [6]. Recently it was shown that an isolated reduction in IHTG in a transgenic mouse model improved both whole body and muscle insulin action, despite compensatory increases in IMCL [7]. However, simultaneous measurements of IMCL, IHTG and visceral/subcutaneous fat in the same individual have never been reported in relation to insulin sensitivity. Therefore, the goals of this project were: 1) to simultaneously measure IMCL, IHTG and visceral fat in the same healthy nondiabetic individual; 2) to determine whether and how these measures were correlated with insulin sensitivity as measured by euglycemic-hyperinsulinemic clamps; 3) to examine whether these fat stores (IHTG, IMCL, visceral/subcutaneous fat) are correlated with plasma leptin levels.

Methods

1. Subjects:

1). Ten non-obese subjects (N=10, 9 males, 1 females; BMI=25.6±2.8) were studied. None of the subjects were professional athletes.

2. MR Methods :

^{1}H MRI and MRS: All MR measurements were done on a 1.5 T GE Signa scanner. Prior to MR spectroscopic measurements, spin echo MR images [TR/TE= 400/8 msec] were obtained in calf and liver. The quantification was done using internal water reference after correcting T1 and T2 [2,8].

IHTG content: IHTG content was obtained using water suppressed ^{1}H MRS using single voxel STEAM [TR/TE=5000/12 msec] with a GE body coil. Typical voxel size was ~ 35 cc.

IMCL content of soleus: The right calf was positioned in a linear GE calf coil. Single voxel STEAM sequence (TR/TE = 2000/24 msec) was used. Typical voxel size was 1.5~2.5 cc.

Quantification of body fat: In all subjects subcutaneous and visceral fat in the region of L3-L4 (in 6 cm slab) around umbilicus were assessed from T1-weighted axial images.

3. Euglycemic-hyperinsulinemic Clamps:

Subjects were fasted overnight and underwent a 5 hour constant insulin (40 mU/m2-min) infusion with variable infusion of 20% dextrose. The Rd [glucose disappearance rates] during euglycemia (5mM) were obtained as a measure of whole-body insulin sensitivity, by infusion of HPLC-purified, tritium-labeled glucose. Plasma leptin levels were measured by immunoassay (ELISA kit, Linco Research, St. Charles, MO).

Results and Discussion

Intrahepatic/myocellular lipid and visceral/subcutaneous fat content (L3/L4) are presented in Table 1, together with glucose uptake (Rd)[post inf. Time:120-150 minutes] and plasma leptin levels. There were remarkably strong correlations between IHTG and Rd (P<0.001, r=-0.87) and between IHTG and leptin levels (P<0.0001, r=0.98, males only, Fig 1). In addition, positive correlations were observed between IMCL and visceral fat (r=0.64, P=0.05), and between IHTG and visceral fat(r=0.62, P=0.05); however, neither IHTG nor IMCL were correlated with subcutaneous fat. Leptin levels and Rd (r=-0.85, P=0.02) were negatively correlated, and there was a modest correlation between subcutaneous fat content and plasma leptin levels in male subjects (r=0.74, P=0.059). These findings are consistent with previous individual studies. Thus, in these nondiabetic subjects, IHTG was the fat depot with the strongest inverse correlation with insulin sensitivity. This finding is consistent with a rodent model in which decreasing IHTG improved muscle insulin action [7]; however, the mechanism remains to be determined. Leptin is likely to play an important role in regulating intrahepatocellular triglyceride content, and ultimately also peripheral insulin action. The tight correlation between leptin levels and IHTG suggests that leptin resistance may have contributed to the accumulation of tissue TG and ultimately to insulin resistance.

Table 1

N=10	IMCL [mmol/g]	IHTG [mmol/g]	Rd [mg/kg-min]	Plasma leptin[a] [ng/ml]	Sub. Fat (g)[b]	Visc. Fat (g)[b]
9 M, 1 F [mean±SD]	7.0±5.6	10.1±5.6	8.8±2.5	2.4±1.3	609±300	324±208

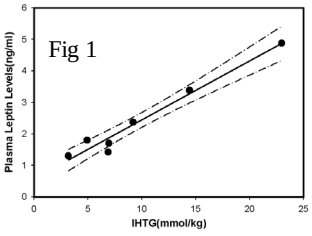

Fig 1

a: in N=7 males

b: fat content in 6 cm of slab located in L3/L4

References

1. McGarry JD, et al, *Diabetes*, 51, 7-18, 2002. 2. Szczepaniak L, et al, *Am J. Physiol*, 276: E977-E989, 1999.
3. Krssak M, et al, *Diabetologia*, 42:113-116, 1999. 4. Banerji M, et al *Int J Obes Relat Metab Disord* 19:846-50, 1995.
5. Ryysy L, et al *Diabetes*,49,749-58,2000. 6. BM Spiegelman, JF Flier, Cell, 104, 531-543. 7. An J, et al. Diabetes 52 (sppl 1):296-OR. 8. Hwang JH et al, JAP, 90:1267,2001.