Pancreatic and hepatic fat and associated metabolic complications in overweight youth

C. A. Syme[1], G. D. Wells[1,2], G. Detzler[1], H-L. M. Cheng[1,2], M. D. Noseworthy[3,4], T. Schirmer[5], B. W. McCrindle[2,6], and J. Hamilton[2,7]

[1]Physiology & Experimental Medicine, The Hospital for Sick Children, Toronto, ON, Canada, [2]University of Toronto, Toronto, ON, Canada, [3]Electrical and Computer Engineering, McMaster University, Hamilton, ON, Canada, [4]Brain-Body Institute, St. Joseph's Healthcare, Hamilton, ON, Canada, [5]Applied Science Laboratory, GE Healthcare, Munich, Germany, [6]Cardiology, The Hospital for Sick Children, Toronto, ON, Canada, [7]Endocrinology, The Hospital for Sick Children, Toronto, ON, Canada

Introduction: Complications of childhood obesity are multiple and include insulin resistance, type 2 diabetes, hypertension, and dyslipidemia. Pancreatic and hepatic steatosis may influence insulin secretion and glucose and lipid metabolism. Only a handful of studies have assessed metabolic outcomes associated with hepatic fat (HF) in youth, and even fewer have studied associations with pancreatic fat (PF). We estimated Indices of PF and HF from in- and out-of-phase images. We hypothesized that HF would be associated with insulin resistance, dyslipidemia and elevated liver enzymes, while PF would be associated with impaired insulin secretion.

Methods: Eleven overweight subjects (body mass index [BMI] > age- and sex-specific 85th percentile; 7 female; aged 9-16 years) with no known liver disease or glucose-altering medication requirements were recruited. Transverse, T1-weighted in- and out-of-phase spoiled gradient-echo imaging of the abdomen was performed during 24 s breath-hold on a 1.5T Signa GE scanner with an 8-channel cardiac coil (field of view=48 cm, TR=150 ms, TE=4.2 (in-phase) or 2.1 (out-of-phase) ms, flip angle=75). Eighteen slices, 10 mm thick with no inter-slice gap, were positioned to cover the volume of the abdomen, including the entire liver and pancreas[1]. Additionally, a single voxel ^{1}H spectrum of the liver was acquired without water suppression during a 16 s breath-hold (Vol=12ml, TE=30ms, TR=4000ms, BW=2500Hz, #sampling points=2048, #averages=4 out of which the first two were discarded as dummy scans). Outer volume SAT bands were turned off to make sure that the voxel sizes from which the water and fat signal were coming were the same, despite the chemical shift displacement. Liver tissue was considered to be homogeneous within the extension of the displacement. The spectrum was reconstructed in GE's spectroscopy analysis software (SAGE), using 2.5 Hz line broadening, and auto-phasing (Figure 1). Hepatic fat (HF) was calculated as HF_{spec}= Sf/(Sf+Sw), where Sf and Sw are the peak areas of fat and water, respectively. From the in- and out-of-phase images, HF was calculated as $HF_{in/out}=(SI_{in} - SI_{out})/(2\times SI_{in})$, where SI is signal intensity in a region of interest with the same size and position as the voxel used for spectroscopy. Pancreatic fat (PF, Figure 2) was similarly assessed using the mean of three such calculations from the head, body and tail of the pancreas[2]. Intra-abdominal fat relative to abdominal volume was estimated from a 5 mm-thick T1 axial slice at L4/L5. Prior to MR assessment, fasting blood work was collected (glucose and lipid metabolism and liver enzymes) and a 2-hour oral glucose tolerance test was performed with sampling of glucose and insulin every 30 minutes. Area-under-the-curve (AUC) insulin, HOMA-IR and whole body insulin sensitivity index (WBISI) were calculated.

Figure 1. Sample spectrum from the liver showing Sw and Sf (left) and a close-up of Sf (right)

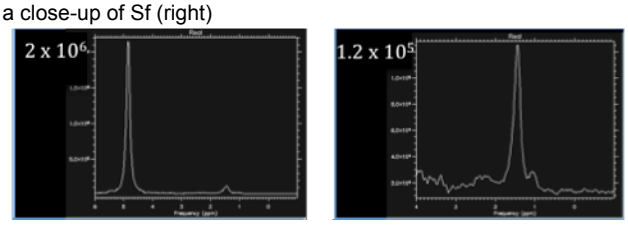
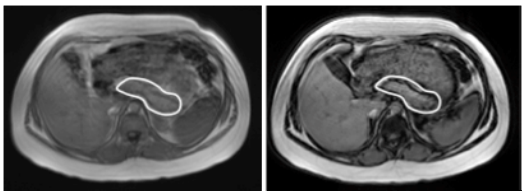


Figure 2. Body and tail of the pancreas outlined on in- and out-of-phase images.



Results: HF_{spec} ranged from 4 to 18%. A strong correlation was observed between HF_{spec} and $HF_{in/out}$ (R^2=0.88, P<0.0001). $HF_{in/out}$ and $PF_{in/out}$ correlated with each other (R^2=0.54, P=0.01), but PF was less than HF (P=0.009). Neither HF nor PF correlated with intra-abdominal fat or BMI z-score. Correlations between fat measures and metabolic parameters are shown in Table 1.

	Hepatic Fat		Pancreatic Fat		Intra-abdominal fat/ abdominal volume		BMI-z score	
	R^2	P	R^2	P	R^2	P	R^2	P
Triglycerides	**0.55 (+)**	**0.009**	**0.62 (+)**	**0.004**	0.04 (-)	0.55	0.22 (+)	0.14
HDL-cholesterol	0.14 (-)	0.25	0.05 (-)	0.50	0.01 (+)	0.72	0.005 (-)	0.84
LDL-cholesterol	0.006 (+)	0.82	0.04 (-)	0.57	0.009 (-)	0.78	0.10 (-)	0.34
Total cholesterol	0.03 (+)	0.60	0.004 (+)	0.85	0.01 (-)	0.76	0.005 (-)	0.83
ALP	0.09 (+)	0.36	0.31 (+)	0.07	0.0004 (+)	0.95	0.07 (+)	0.42
ALT	0.18 (+)	0.22	**0.45 (+)**	**0.03**	0.13 (-)	0.31	0.08 (+)	0.42
AST	0.34 (+)	0.08	0.38 (+)	0.06	0.11 (-)	0.34	0.05 (+)	0.53
Glucose	0.007 (-)	0.81	0.07 (+)	0.45	0.05 (+)	0.49	0.11 (+)	0.32
Insulin	**0.72 (+)**	**0.0009**	**0.57 (+)**	**0.007**	0.05 (-)	0.50	0.17 (+)	0.20
HOMA-IR	**0.69 (+)**	**0.002**	**0.56 (+)**	**0.008**	0.05 (-)	0.51	0.18 (+)	0.20
AUC insulin	**0.64 (+)**	**0.003**	**0.56 (+)**	**0.008**	0.05 (-)	0.51	0.27 (+)	0.10
WBISI	0.28 (-)	0.09	**0.60 (-)**	**0.005**	0.02 (-)	0.70	**0.42 (-)**	**0.03**

Table 1. Metabolic correlates of fat indices. (+) or (-) indicate direction of association.

Discussion: Pancreatic and hepatic fat appear to have complementary clinical consequences. PF was associated with increased, rather than impaired insulin secretion. This finding is in agreement with the one other study that has made this assessment in normal and overweight healthy youth[3], and suggests that PF deposition does not lead to decreased insulin secretion during early stages of metabolic disturbances. Our findings relating HF to insulin resistance and triglycerides are in agreement with other studies in obese youth, however we did not observe previously reported associations with cholesterol or elevated hepatic enzymes. The latter suggests that perhaps early HF accumulation may influence glucose metabolism before hepatic transaminases become elevated. The lack of associations between intra-abdominal fat or BMI z-score and these metabolic parameters highlights the importance of discriminating between fat distribution rather than fat quantity alone. The current study reveals the potential to index simultaneously ectopic fat in two organs important for glucose and lipid metabolism.

References: [1]Borra RJ et al. Radiology 2009; [2]Schwenzer NF et al. Invest Radiol 2008; [3]Kovanlikaya A et al. Pediatr Radiol 2005.

The HISTORY study (High Impact Strategies Towards Overweight Reduction in Youth) is funded by the Canadian Institutes of Health Research, and CS is funded by the Heart and Stroke Foundation of Ontario.