Non-Invasive Assessment of Inflammation in White Adipose Tissue Using Magnetic Resonance Imaging

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Introduction: Obesity is associated with alteration in adipocyte metabolic/endocrine functions such as lipolysis, adipokine (i.e. leptin, adiponectin) and cytokine production (TNFa, IL-6). Adipocyte inflammation has taken a prominent role in mediating metabolic/endocrine alterations which result in insulin resistance and dyslipidemia. Ultrasmall Superparamagnetic Iron Oxide (USPIO) imaging contrast agents have previously been used as a surrogate for macrophage load and/or inflammatory activity (1,2). Therefore the aim of this study was to assess the feasibility of non-invasively imaging macrophage and/or activity as a surrogate for inflammation in various adipose tissue depots.

Methods: Spin echo, multi-slice, coronal scout imaging (TE/TR=10.6/500 ms, FOV=8 cm, NEX=1, Matrix=128x128) and gradient echo, multi-slice, coronal high resolution imaging (TE/TR=7/438 ms, FOV=8 cm, flip angle=30 degrees, Matrix=256x256) of ob/ob mice (~60-65g) was performed at 4.7T. Immediately after baseline imaging mice were divided into Control (-USPIO), Combidex® (USPIO, 1000 umol/kg), and Feridex® (SPIO, 1000 umol/kg) groups and 2 doses of contrast agent were administered 24 hr apart. Imaging was performed at 24, 48, 72, and 96 hrs post-dosing. Fat pads (subcutaneous and peritoneal) were harvested for quantitative analysis of iron uptake and for Perl's iron staining and CD68 macrophage immunohistochemistry.

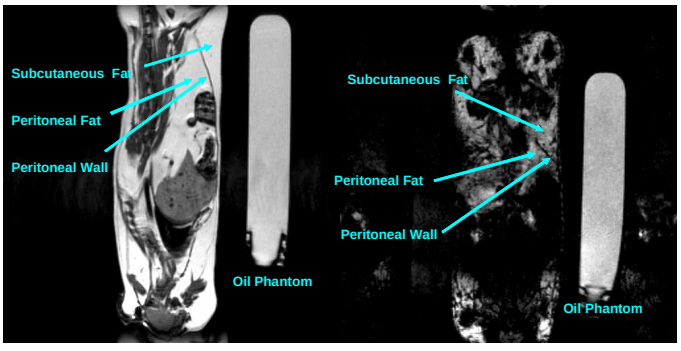
Results: Combidex® appeared to be the optimal iron oxide contrast agent to use for MRI examination. Figure 1 illustrates significant signal loss in fat depots at 24 hr post-dosing. A minimum of 2 doses of Combidex® was required and imaging was required to be performed at least 48 hrs post-final dose in ob/ob mice in order to allow for blood pool clearance of the imaging agent. After 48 hrs, signal loss was ~20-35% and USPIO uptake in the adipose depots was verified via absolute Fe analysis. Intraperitoneal fat had a much greater prevalence for macrophages than did the subcutaneous fat. It also appeared that the USPIO had greater specificity for macrophage (Figure 2) in the intraperitoneal fat than in the subcutaneous fat.

Summary: This study represents, to the author's best knowledge, the first time that inflammation of adipose tissue has been examined non-invasively. Future studies include examining PPARγ and/or PPARδ agonists which are known to decrease macrophage infiltration and reduce inflammatory biomarkers in this tissue.

References:

1) Ruehm SG et al. *Circulation* 103:415, 2001
2) Yancy AD et al. *JMRI* 21:432, 2005

Figure 1



Baseline Post-Combidex

Figure 2