A Specific Aims

Obesity is a growing epidemic in the United States, affecting multiple health outcomes in children, adolescents, and adults [2–5]. This increased risk includes metabolic disturbances such as glucose intolerance, insulin resistance, hyperlipidemia, diabetes mellitus, and cardiovascular and liver diseases [6–21]. Increasing data suggest that the link between obesity and poor health outcome is related to the buildup of fat in specific fat depots (e.g. visceral fat inside the abdominal cavity) and/or infiltration of fat into muscle, liver, and other organs.

The assessment of fat distribution (and not simply total body fat) has become an important component of risk assessment, intervention, the evaluation of new therapeutic approaches, and basic research on the mechanisms explaining why obesity is related to poor health outcome. Magnetic resonance imaging (MRI) is potentially the most appropriate modality for such an assessment, because it (1) is inherently three-dimensional and therefore can resolve the relevant fat depots, organs, and tissues, (2) provides an extremely sensitive mechanism for separating water and fat, and (3) is completely non-invasive and involves no ionizing radiation, leading to indefinite repeatability and ultra-low risk for longitudinal studies in humans.

MRI is becoming more frequently used in obesity research, but current protocols have several drawbacks including: (1) long and/or multiple breathholds required for 3D coverage, leading to patient discomfort and potential motion-related errors, (2) long scan-times and the high-cost of magnet time (∼$500 per hour), and (3) measurements are limited to adipose tissue volume or fat signal fraction rather than the potentially more relevant quantity of fat mass. In addition, in vivo MRI-measurement of total organ fat has never fully been validated against a gold standard such as chemical analysis.

Our overall objective is therefore to develop, optimize, and fully validate a new MRI-based test that provides accurate regional quantification of abdominal fat in adipose tissue, critical organs, and skeletal muscle. The new test will consist of a single 3D scan of the entire abdomen with $3 \times 4 \times 4 \text{ mm}^3$ spatial resolution, and an imaging time of 16 seconds (performed during a breathhold). Calibration scans will require two to three additional breathholds, and are expected to drastically improve the accuracy of computed fat mass. Validation will be performed in whole animals, using necropsy and chemical analysis as the gold standard.

Our specific aims are:

A.1 To develop and optimize MRI calibration and postprocessing methods for quantifying fat mass on a voxel-by-voxel basis.

We will develop several signal-intensity calibration schemes that enable the quantification of fat mass on a voxel-by-voxel basis using 3D IDEAL-SPGR, and identify the optimal one. Calibrations will incorporate RF transmit/receive variation and $T_1$ variation, and will enable the use of SNR-optimal imaging flip angles. Tissue proton density will be used as an intermediate metric, for testing in abdomen-sized phantoms, and in the subcutaneous fat of animals in the Testing Group (see below). In vivo endpoints will include: voxel-by-voxel fat mass, and total fat mass within regions of adipose tissue, whole organs, and regions of skeletal muscle.

A.2 To validate the proposed methods in a swine model using post-mortem analysis as the reference.

We will study 15 adult farm pigs with a range of abdominal sizes comparable in circumference to obese humans, which will be divided into a 5 animal Testing Group (for the pilot evaluation and possible refinement of methods described in Aim #1) and a 10 animal Validation Group. The proposed MRI methods will be used to quantify fat mass within seven well-defined regions of interest: two regions of adipose tissue, three whole organs, and two regions of skeletal muscle. MRI will be followed by euthanasia, necropsy, and chemical analysis of samples matching the MRI volumes.

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The project builds a strong interdisciplinary approach based on Krishna Nayak’s expertise in the development of rapid MRI techniques and Michael Goran’s expertise in body composition assessment and validation; and will bring together their complementary research groups with the common goal of creating a valuable new tool for clinical investigations of diabetes and associated diseases.