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Adipose Tissue MRI for Quantitative Measurement of Central Obesity

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Abstract

Purpose—To validate adipose tissue magnetic resonance imaging (atMRI) for rapid, quantitative volumetry of visceral adipose tissue (VAT) and total adipose tissue (TAT).

Materials and Methods—Data was acquired on normal adults and clinically-overweight girls with IRB approval/parental consent using sagittal 6-echo 3D-SPGR (26-sec single-breath-hold) at 3T. Fat-fraction images were reconstructed with quantitative corrections, permitting measurement of a physiologically-based fat-fraction threshold in normals to identify adipose tissue, for automated measurement of TAT and semi-automated measurement of VAT. TAT accuracy was validated using oil phantoms and in vivo TAT/VAT measurements validated with manual segmentation. Group comparisons were performed between normals and overweight girls using TAT, VAT, VAT-TAT-ratio (VTR), body-mass-index (BMI), waist circumference, and waist-hip-ratio (WHR).

Results—Oil phantom measurements were highly accurate (< 3% error). The measured adipose fat-fraction threshold was $96\% \pm 2\%$. VAT and TAT correlated strongly to manual segmentation (normals $r^2 = 0.96$, overweight girls $r^2 = 0.99$). VAT segmentation required 30 ± 11 minutes/subject (14 ± 5 sec/slice) using atMRI, versus 216 ± 73 minutes/subject (99 ± 31 sec/slice) manually. Group discrimination was significant using WHR ($p < 0.001$) and VTR ($p = 0.004$).

Conclusion—The atMRI technique permits rapid, accurate measurements of TAT, VAT and VTR.

Keywords

adipose tissue; body mass index; metabolic syndrome; central obesity

INTRODUCTION

Metabolic syndrome is a “clustering” of metabolic abnormalities and cardiovascular risk factors, including obesity, type II diabetes, fatty liver disease and coronary artery disease, afflicting an estimated 47 million Americans (1). People suffering from metabolic syndrome are three times more likely to have a heart attack or stroke, have five-fold greater risk of type II diabetes, are at progressive risk of severe liver disease including cirrhosis, liver failure and hepatocellular carcinoma, and have increased rates of cardiovascular disease and premature death (2,3). While the underlying causes of metabolic syndrome are not fully understood, central obesity i.e. excessive “visceral” adipose tissue (VAT) inside the abdomen, is known to be a major risk factor (4–6). In other words, both the *amount* and the *distribution* of abdominal fat influence the risk; therefore any biomarker for central obesity must provide information about both to be effective. Ideally, measurement of central obesity should have a direct physiological basis for maximal clinical relevance, requiring a quantitative technique that is independent of platform and protocol.

Unfortunately, no clinical consensus exists on diagnostic criteria for central obesity (2). Anthropometric biomarkers for central obesity such as waist circumference, waist-hip ratio (WHR), and body mass index (BMI) (2,7,8) are widely used clinically, as per guidelines introduced by the National Cholesterol Education Program’s Adult Treatment Panel (ATP III) (9) and revised by the International Diabetes Federation (2). However, these anthropometric measures are not direct physiological measurements of central obesity, but rather indirect surrogates that fail to accurately measure VAT volume (8,10–13). Anthropometric measures are also highly prone to systematic error due to methodological variability in anatomic site, respiratory phase, and even meal timings (14,15).

Direct measurement of VAT volume using diagnostic imaging techniques is clearly preferable to anthropometric surrogates, and satisfies the requirement of a physiological basis. For example, X-ray computed tomography (CT) can provide full abdominal and pelvic coverage in only a few seconds’ acquisition time (16). Unfortunately, CT exposes the patient to ionizing radiation, limiting its clinical use to diagnosing acute patient illnesses. A safe alternative is T1-weighted magnetic resonance imaging (MRI) (10,17), which delivers no ionizing radiation. However, for every subject, both CT and T1-weighted MRI require many hours of tedious manual segmentation of VAT from subcutaneous adipose tissue (SCAT) and non-adipose tissues, a process that is cost-inefficient and highly prone to systematic error (10,16–18). Alternatively, histogram-based thresholding can be used to estimate adipose tissue volume from MR images (19–22), but such methods are purely qualitative due to partial volume effects, off-resonance effects, and magnetic susceptibility. While CT and MRI methods have been validated as biomarkers for central obesity in small-scale research studies (8,10,11,16), neither technique has found widespread clinical use as a replacement for anthropometric measures.

Adipose tissue segmentation is considerably more efficient and accurate if the fat signal can be isolated during image acquisition. Among techniques for direct imaging of fat, chemical-shift-based MRI (23–27) has been shown to have superior fat-water separation quality (28–30). These methods exploit the resonance frequency difference between fat and water to provide separate, co-registered images of water, fat and “fat-fraction” (31) and have been validated in liver and pancreas (32,33). In principle, these chemical-shift fat/water imaging methods have great potential for automated adipose tissue segmentation (34–36) because adipose tissue may be rapidly separated from non-adipose tissue using only a simple fat-fraction threshold (typically 50%). The time efficiency of using fat-fraction values to segment adipose tissue is a major advantage of chemical-shift methods over manual segmentation. However, prior to thresholding, fat-fraction maps require empirical masking

to remove noise in background areas, air cavities, and signal voids, partly negating the speed advantage.

Furthermore, the accuracy of chemical shift methods is confounded by a number of physical factors including T1 and T2* relaxation effects (31,37,38), spectral complexity of fat (39,40), noise related bias (31) and the effects of eddy currents (41) which if left uncorrected will result in large and significant errors in fat-fraction values (32,39). Since most studies define adipose tissue as having fat-fraction values of 50% or higher, these errors directly impact the accuracy of VAT or total adipose tissue (TAT) volume estimation, particularly in areas where partial volume effects occur. A chemical-shift fat/water technique which can correct for all confounding factors in fat-fraction measurement is therefore a requirement for truly quantitative adipose tissue measurements. Presently, only two such techniques are reported in the literature (37,42,43), both requiring multi-echo data acquisition to accurately model T2* relaxation and the multi-peak spectrum of the fat signal (37,40). Of these, the technique employing complex (magnitude and phase) data for image reconstruction (37,43) provides a full fat-fraction dynamic range of 0–100%, making this approach ideally suited for adipose tissue quantification.

Finally, a 50% fat-fraction threshold implicitly assumes that adipose tissue has a maximum fat fraction of 100%. However, this common assumption is incorrect since in vivo adipose tissue typically contains blood vessels, cell organelles, membranes, and other non-lipid components. The true maximum fat-fraction of adipose tissue will therefore be some value $\eta_{MAX} < 100\%$, and a fat-fraction threshold of $\eta_{MAX}/2$ would be a physiologically meaningful threshold for masking voxels as adipose tissue or not.

In this work, we seek to overcome the obstacles discussed above, which have precluded clinical adoption of chemical shift fat-water MRI for accurate quantification of central obesity. We do so by combining four technical innovations: First, we implement an accelerated multi-echo chemical-shift fat/water imaging protocol on a 3T scanner with a 32-channel coil to acquire near-isotropic, high-resolution data over the entire abdomen and pelvis within a single 26-second breath-hold. Second, we employ T2* corrected complex-data reconstruction with spectral modeling of fat to obtain quantitative fat-fraction maps with full dynamic range of 0 – 100% (37,43). Third, we apply a clustering algorithm (44) to automatically and robustly remove noise from the fat-fraction maps, without any need for empirical masking. Finally, we estimate η_{MAX} directly from the data, and use it for thresholding the noise-masked fat-fraction image to generate an accurate binary mask of adipose tissue, or “fat mask”. The result is a new technique, adipose tissue MRI (atMRI), which permits fully automated measurement of the Total Adipose Tissue (TAT) volume and rapid, semi-automated measurement of VAT volume. We also validate the quantitative accuracy of TAT measurement from atMRI using oil phantoms, and validate TAT and VAT measurements in vivo against fully-manual segmentation, in both normal adult subjects and a target population of clinically overweight (BMI-for-age > 85th percentile) (45) adolescent females considered at-risk for developing metabolic syndrome as adults (waist circumference > 80 cm) (2). Finally, we define the VAT-TAT-ratio (VTR) and assess how well it compares to TAT, VAT, and the anthropometric measures of BMI, WHR and waist circumference in discriminating between different subject populations.

MATERIALS AND METHODS

Image Acquisition and Reconstruction

MRI acquisitions were performed on a clinical 3.0 T MRI scanner (MR 750, GE Healthcare, Waukesha WI) using a 32-channel phased-array body coil (Neocoil, Pewaukee WI). All images were acquired using an investigational 3D multi-echo spoiled gradient-echo (SPGR)

sequence that acquired a single sagittal slab (24) with 6 echoes and a low flip angle of 3° to minimize T1-weighting bias (31).

Phantom data were acquired with TR = 7.3 ms, BW = ± 200 kHz, and echo train length (ETL) = 3 (2 shots), first TE = 1.0 ms, and echo spacing = 1.6 ms in each shot. The data was acquired over $44.8 \text{ cm} \times 31.4 \text{ cm} \times 18.4 \text{ cm}$ FOV with $224 \times 157 \times 92$ matrix, for true spatial resolution of $2.0 \times 2.0 \times 2.0 \text{ mm}^3$, interpolated to $1.8 \times 1.8 \times 1.0 \text{ mm}^3$ through zero-filling. Total scan time was 35 sec using auto-calibrated parallel imaging (ARC) (46) with an acceleration factor of 5.09.

In vivo data were acquired with TR = 9.0 ms, BW = ± 167 kHz, and ETL = 6 (1 shot), first TE = 0.8 ms and echo spacing = 1.2 ms. The data was acquired over $48.0 \text{ cm} \times 38.4 \text{ cm} \times 46.8 \text{ cm}$ FOV with $148 \times 118 \times 156$ matrix for true spatial resolution of $3.2 \times 3.2 \times 3.0 \text{ mm}^3$, interpolated to $1.9 \times 1.9 \times 1.5 \text{ mm}^3$ through zero-filling. Total scan time was 26 sec using ARC (46) with an acceleration factor of 5.32.

Fat and water images were reconstructed using complex data (43,47) using spectral modeling of fat (40) T2* correction (37) and correction for eddy current-induced phase shifts (41). Quantitative fat-fraction maps with full range of 0–100% were subsequently generated using a magnitude discrimination technique to minimize noise bias (31).

Noise Thresholding

The raw fat-fraction image contains random noise in the background and air filled cavities, arising from the definition of fat-fraction as an image ratio. In order to mask this noise, a k-means clustering algorithm (44) was used to segment the 3D volume by assigning each voxel to either a single noise cluster or one of 5 possible tissue clusters using MATLAB (The Mathworks, Natick MA). The algorithm used the fat, water and fat-fraction images as inputs, after empirical determination of optimal seed values (48) for the noise and tissue clusters, which differed between the phantom and the in vivo data. Voxels containing background noise and air cavities were automatically isolated with the algorithm and used to define a noise mask, which was applied to the fat-fraction image to effectively and automatically filter out the noisy voxels.

Phantom Validation Experiment

A phantom comprised of nine bottles of peanut oil, with precisely known oil volumes (250 cc, 500 cc, and 750 cc) and increasing surface area complexity (oil, oil with 2% agar spheres, and oil with 2% agar spheres, and glass rods) was constructed (Figure 1). The purpose of the phantom was to test the performance of the TAT estimation algorithm in the presence of increasing partial volume effects. Three acquisitions were performed, each on a trio of bottles with identical composition, but increasing oil volumes (i.e., each row in Figure 1). The total volume of oil for each of the three acquisitions was constant (1500 cc).

The noise thresholding algorithm described above was used to suppress background noise and signal voids from glass and air cavities automatically. The maximum fat-fraction value η_{MAX} in oil was then measured by drawing ROIs within each bottle, and found to be 0.997 ± 0.005 (standard deviation across bottles). The fat mask was then defined as all voxels of the noise-masked fat-fraction map with values greater than or equal to $0.498 (\eta_{MAX}/2)$.

TAT volume for each bottle was obtained by multiplying the number of voxels in the fat mask for the bottle of interest by the interpolated volume of a single voxel. Since bottles were imaged in groups of three, ROIs to isolate each bottle were drawn and applied to every slice. Total processing time of raw fat and water images to TAT volume was < 5 min and

required no user intervention, apart from initial bottle ROI placement and measurement of η_{MAX} .

In vivo Experiment – VAT Volume

Fifteen adult normal subjects (8 male, 7 female, 14 Caucasian, 1 African-American) and ten clinically overweight (BMI-for-age above the 85th percentile) (45) adolescent females (7 African-American, 1 Hispanic, 2 Caucasian) were recruited for this HIPAA compliant study, after IRB approval and informed consent/assent and parental consent where necessary. The average age of the normal subjects was 28.2 ± 10.2 years (range = 19 – 60) and the average age of the adolescent females was 13.0 ± 0.8 years (range = 12 – 14). The BMI of the normal subjects was 24.6 ± 4.2 (range = 20.6 – 34.9) and the BMI of the overweight subjects was 30.2 ± 5.5 (range = 24.9 – 42.3).

MR images were acquired on each subject in a single breath-hold, with patients positioned feet first in the MR scanner, and arms above their heads whenever patient comfort permitted. Coil position was verified using localizers for full abdominal coverage from liver dome to pelvic floor (Figure 2). All images were reformatted to axial view for subsequent processing. The raw fat-fraction images were noise-masked using the thresholding algorithm described above. Examples of fat-fraction images before and after noise masking are illustrated in Figures 3a and 3b, respectively.

To estimate the true maximum fat-fraction value η_{MAX} , ROI measurements were placed using ImageJ (National Institutes of Health, Bethesda MD) in a large anterior, inferior region of homogenous subcutaneous adipose tissue (SCAT) for each normal subject. The mean fat-fraction values in these ROIs were averaged across subjects to obtain a “global” estimate of η_{MAX} which was used in all subsequent analyses on both normals and overweight subjects. The “fat mask” was then defined for each subject as all voxels of their noise-masked fat-fraction map with values greater than or equal to $\eta_{MAX}/2$ (Figure 3c). The volume of TAT was then obtained by counting the number of voxels in the fat mask and multiplying by the interpolated single-voxel volume. Arms and breast tissue were manually trimmed from the TAT mask in several cases where overweight subjects could not comply with requested posture (arms above the head during scanning) due to discomfort.

For VAT segmentation, the fat mask was loaded in ImageJ (National Institutes of Health, Bethesda MD). VAT was delineated by drawing a freehand selection, avoiding vertebrae and intramuscular fat (Figure 4a). The starting and ending slices were chosen identically to the manual segmentation volume (see validation section below) for direct comparison. The volume of VAT was obtained by counting all nonzero voxels within the selection on each slice, and multiplying by the interpolated single-voxel volume. The VAT-TAT ratio (VTR) was also calculated by dividing VAT volume by TAT volume.

Validation in Subjects Using Manual Segmentation

VAT and TAT were also manually segmented for each subject using SliceOMatic v4.3 (Tomovision, Quebec). VAT was delineated using the fat-only image, reformatted to the axial plane. The segmentation volume was defined using anatomical landmarks for consistency: the most inferior slice chosen so the top of the sacrum is first clearly delineated from VAT; the most superior slice was chosen so the heart is just coming in to view, to minimize inclusion of epicardial fat and to ensure inclusion of VAT internal to the peripheral appearing lung tissue. Within the target volume, fat within the vertebral bodies, intramuscular fat, and intra-renal fat were excluded from VAT, but included with the TAT measurement (Figure 4b). The water-only image was used to resolve ambiguous regions, such as artifacts or suspected areas of stool, which appeared bright on both fat and water

images. The volume of VAT was then measured by integrating the areas within the compartment. The VTR was also calculated for comparison purposes.

Anthropometric Measurements

Each subject's height, weight and waist and hip circumferences were measured prior to scanning. For waist, the measuring tape was positioned mid-way between the top of the hip bone and the bottom of the rib cage, with relaxed stomach, breathing out. For hip, the measurement was made at the widest part of the buttocks. The BMI and waist-hip-ratio (WHR) were also calculated from these values.

Statistical Analysis

For the phantom experiments, linear regression was used to assess the accuracy of TAT volume measured using atMRI, relative to the known volume of oil in each bottle. For in vivo experiments, linear regression was used to assess how well the atMRI method predicted manual TAT volume and VAT volume. Pearson coefficients were calculated to assess the correlation of anthropometric measures to manual VAT volume, and compare to semi-automated VAT volume obtained using atMRI. Finally, a two-tailed t-test was used to investigate significant differences in TAT, VAT, VTR, BMI, WHR, and waist circumference between the normal adults and the overweight girls. The F-statistic was computed for each measure, to determine whether the variances were equal or unequal, and the t-test was computed with either the homoscedastic or heteroscedastic assumption accordingly.

RESULTS

In the oil phantom experiment, atMRI accurately measured the volume of oil in each of the nine bottles. The linear fit had $r^2 = 0.991$ for the three bottles of oil, $r^2 = 0.996$ for the three bottles containing oil and agar spheres, $r^2 = 0.996$ for the three bottles containing oil, agar spheres and glass rods, and $r^2 = 0.992$ for all nine bottles, demonstrating that the accuracy of the measurement was unaffected by increasing surface area of fat-water and fat-void boundaries (Figure 5). The total volume of oil in each acquisition (three bottles) was 1517 cc for oil only, 1459 cc for oil and agar, and 1493 cc for oil, agar and void, with maximum percentage error of 2.75% relative to the known oil volume of 1500 cc. The measured volume of all nine oil bottles was 4468 cc, a percentage error of 0.71% relative to total oil volume of 4500 cc. Linear regression fit parameters for the TAT phantom measurements in are summarized in Table 1.

The average maximum fat-fraction threshold value η_{MAX} across all normal subjects was $96\% \pm 2\%$. The average time required for manual segmentation over all subjects was 216.0 ± 72.5 min (99 ± 31 sec/slice, range 90 – 300 min) versus 30.2 ± 11.0 min (14 ± 5 sec/slice, range 16 – 60 min) for semiautomatic segmentation. Detailed comparisons of segmentation time in minutes/study and seconds/slice are summarized in Table 2, for normal subjects and overweight adolescent females.

In adult normals, measurements using atMRI were predictive of manual measurements for TAT ($r^2 = 0.99$), and VAT ($r^2 = 0.96$). These correlations are illustrated in Figures 6a and 6b. For overweight girls, measurements using atMRI were likewise predictive of manual measurements for TAT ($r^2 = 0.99$) and VAT ($r^2 = 0.99$). These correlations are illustrated in Figures 6c and 6d. All linear regression fit parameters for in vivo measurements in adult normals and overweight girls are summarized in Table 1.

In general, anthropometric measures had substantially poorer correlation to manual VAT than atMRI-derived VAT, in both normals and overweight girls. In normal adults, waist-hip

ratio (WHR) was the poorest correlate to manual VAT ($r = 0.16$), followed by BMI ($r = 0.39$). In overweight girls, WHR was even worse ($r = 0.08$) but BMI was a little better ($r = 0.51$). In both groups, waist circumference was the best correlate ($r = 0.56$) to manual VAT, but even this fell far short of atMRI measurement of VAT ($r = 0.96$).

Among anthropometric measures, waist circumference did not discriminate between the two groups of subjects ($p = 0.07$), but there was a significant difference between groups for WHR ($p < 0.001$). BMI also was significantly different ($p = 0.009$) between groups, as expected, since BMI-for-age was used as selection criteria for the overweight girls. Likewise, there was no significant difference in VAT ($p = 0.81$) or TAT ($p = 0.09$) between the groups, but VTR did have a significant difference ($p = 0.004$). Group comparisons are illustrated as box and whisker plots in Figure 7.

DISCUSSION

In this work we have demonstrated that the atMRI technique is a direct, quantitative measurement of central obesity that is feasible in a clinical setting, requiring a single 26-sec breath-hold acquisition and as little as 15 minutes of user intervention. On average, this represents about an order of magnitude less supervised effort compared to manual segmentation of VAT and SCAT, and the time can be further reduced in practice with increased operator experience, patient compliance regarding arm position, and more sophisticated morphological processing or software.

The volume measurements obtained from atMRI correlated very strongly to manual measurements, however the measurements were consistently higher using manual segmentation, by a small but statistically significant amount. The difference may arise from the qualitative nature of manual segmentation, which uses MR signal intensity as an indicator of fat content rather than quantitative fat-fraction values. When delineating adipose tissue structures by hand, non-adipose structures with similar signal intensities may be falsely included, resulting in a small, but statistically significant overestimation of the adipose volume. Given the excellent agreement of the fat volumes in the phantoms, it is possible that in vivo, the automated segmentation may actually be more accurate than the manual segmentation.

The maximum fat-fraction threshold value η_{MAX} was a global value, averaged across the normal subjects. However in principle η_{MAX} can be determined on a per-subject basis, with the advantage of being fully automated and more reproducible compared to the ROI method in SCAT. This technique is fully capable of using individual values of η_{MAX} on a per-subject basis. Regardless of the specific methodology used, it is important for clinical validity that it be physiologically meaningful and not an arbitrary choice. We are further investigating further the impact of alternate methodologies for η_{MAX} measurement on TAT volume and VTR.

As expected, the correlation of the direct VAT measurement using atMRI to the gold standard of manual VAT segmentation was superior to anthropometric metrics. However, it should be noted that the anthropometric measures should still be retained as supplementary measures, especially given their long history, low cost, and fundamental ease of measurement. For example, WHR has been shown to have clinical relevance to insulin resistance (5) and female obesity, particularly for African-American women (11–13). However, in other studies, WHR has been found less effective than simple waist circumference in correlating with VAT (7,8). These contradictory results may arise from the severe effect that methodological variability has on any anthropometric measurement (14,15). As biomarkers of central obesity, anthropometric measures fall short, but their poor

correlation to VAT volume may be an advantage in that they represent independent measures of abdominal disease beyond central obesity. If used in conjunction with VAT, they may help provide a broader picture of disease states than just central obesity alone.

The use of VTR, or effective abdominal VAT fraction, also provides an alternative metric to characterize central obesity than VAT volume alone. The advantage of VTR over VAT is that it is a standardized metric, bounded from 0 to 1, facilitating inter-subject comparisons without confounding factors of height and weight. VTR also was able to significantly discriminate between adult normal and overweight adolescent female groups, despite small sample size, unlike VAT and TAT. This suggests that VTR may have more clinical utility in disease screening and treatment monitoring than VAT alone, and merits further investigation.

In the literature, other groups have also used fat-fraction maps for identifying adipose tissue (34–36). However, these methods have coarse spatial resolution, which permits whole-body adipose tissue characterization (20,35), but the accuracy of adipose tissue volume measurement is undermined by partial-volume effects. In addition, they do not employ quantitative fat/water reconstruction with error corrections for confounding factors as defined above. Thus, even if a fat-fraction threshold is used to define adipose tissue, the fat-fraction values will be only semi-quantitative, potentially leading to systematic errors. The routine use of 50% rather than in vivo estimation of a physiological fat-fraction threshold may also bias the final volume measurements. In the absence of a quantitative fat-water reconstruction, however, estimation of η_{MAX} will also be semi-quantitative. Ultimately, only a quantitative technique such as atMRI will suffice for accurate adipose volume measurements, and quantification of central obesity.

Regardless of the degree of quantitative accuracy, most studies reported in the literature do report high agreement with manual VAT segmentation. However, all such studies (including this study) make the comparison between the new technique and manual methodology using local data, and the methodology of the manual measurements in particular is often left unspecified. As adiposity imaging matures, a clear need is developing for a consensus data set or atlas of visceral fat in the abdomen and pelvis against which all algorithms can be evaluated.

One potential limitation of our technique is the breath-hold requirement, which at 26-seconds is acceptable for a normal subject but may be difficult for more obese patients. Though the vast majority of our subjects were able to maintain the full 26-second breath-hold, not all subjects may be able to tolerate that length of time. In the very few cases (<2) where subjects could not hold their breath for the complete 26 seconds, motion artifacts were relatively minor, partly because we coached them using 2–3 inspirations prior to scan. To accommodate a subject who cannot hold their breath for this period, we can in principle sacrifice spatial resolution and acquire data in less time. This would result in more partial volume effects between fat and water and would degrade the accuracy of the adipose tissue measurements, but would be preferable to having no data on the patient at all.

The primary limitation of this study is the small sample size ($n = 25$). However, the primary objective was to describe the technical implementation of the imaging acquisition, and to validate the use of atMRI to measure TAT and VAT using a physiologically based automatic masking algorithm that facilitates rapid segmentation. The next logical step in this work is to apply these adiposity metrics to a larger clinical population of patients at risk for metabolic syndrome, which was previously not feasible in the past given the exceedingly high post-processing time requirements of manual segmentation. Inclusion of age and

gender-matched controls will also permit more rigorous evaluation of VTR's effectiveness at discrimination and screening.

In addition, our method does still require manual intervention for segmentation of VAT from TAT. Other groups have demonstrated fully automated VAT segmentation using various morphologic, histogram, and clustering strategies (19,20,34–36,49), which we note are all fully compatible with and complementary to atMRI. However, the quantitative fat-water reconstruction and physiological fat-fraction threshold which atMRI provides remains a prerequisite for central obesity characterization – to be clinically relevant, any automated VAT segmentation method will require truly quantitative TAT assessment first.

In conclusion, adipose tissue MRI (atMRI) is a clinically feasible method for quantifying adipose tissue distribution, with validation in oil phantoms and human subjects. The benefits of atMRI over other adipose imaging methods are the accelerated acquisition, quantitative reconstruction, and physiologically-based threshold, all of which are required for accurate adipose tissue measurements. The fat mask generated by atMRI requires no operator intervention and facilitates rapid segmentation of visceral fat, which permits the calculation of TAT and VAT volumes the VAT-TAT ratio (VTR) in a clinical setting. The atMRI technique thus provides a reliable, non-invasive characterization of central obesity, which plays a central role in metabolic syndrome risk assessment.

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REFERENCES

1. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *Jama*. 2002; 287(3):356–359. [PubMed: 11790215]
2. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. *Lancet*. 2005; 366(9491):1059–1062. [PubMed: 16182882]
3. Stern MP, Williams K, Gonzalez-Villalpando C, Hunt KJ, Haffner SM. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? *Diabetes Care*. 2004; 27(11):2676–2681. [PubMed: 15505004]
4. Bergman RN, Kim SP, Catalano KJ, et al. Why visceral fat is bad: mechanisms of the metabolic syndrome. *Obesity (Silver Spring)*. 2006; 14(Suppl 1):16S–19S. [PubMed: 16642958]
5. Carr DB, Utzschneider KM, Hull RL, et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. *Diabetes*. 2004; 53(8):2087–2094. [PubMed: 15277390]
6. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature*. 2006; 444(7121):881–887. [PubMed: 17167477]
7. Pouliot MC, Despres JP, Lemieux S, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol*. 1994; 73(7):460–468. [PubMed: 8141087]
8. Onat A, Avci GS, Barlan MM, Uyarel H, Uzunlar B, Sansoy V. Measures of abdominal obesity assessed for visceral adiposity and relation to coronary risk. *Int J Obes Relat Metab Disord*. 2004; 28(8):1018–1025. [PubMed: 15197408]

9. Grundy, S. Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Bethesda, MD: National Institutes of Health; 2001. NIH Publication 01–3670
10. Joy T, Kennedy BA, Al-Attar S, Rutt BK, Hegele RA. Predicting abdominal adipose tissue among women with familial partial lipodystrophy. *Metabolism*. 2009; 58(6):828–834. [PubMed: 19375764]
11. Ludescher B, Machann J, Eschweiler GW, et al. Correlation of fat distribution in whole body MRI with generally used anthropometric data. *Invest Radiol*. 2009; 44(11):712–719. [PubMed: 19809346]
12. Conway JM, Chanetsa FF, Wang P. Intraabdominal adipose tissue and anthropometric surrogates in African American women with upper- and lower-body obesity. *Am J Clin Nutr*. 1997; 66(6): 1345–1351. [PubMed: 9394685]
13. Micklesfield LK, Evans J, Norris SA, et al. Dual-energy X-ray Absorptiometry and Anthropometric Estimates of Visceral Fat in Black and White South African Women. *Obesity*. 2009; 17:17.
14. Mason C, Katzmarzyk PT. Variability in waist circumference measurements according to anatomic measurement site. *Obesity (Silver Spring)*. 2009; 17(9):1789–1795. [PubMed: 19343017]
15. Agarwal SK, Misra A, Aggarwal P, et al. Waist circumference measurement by site, posture, respiratory phase, and meal time: implications for methodology. *Obesity (Silver Spring)*. 2009; 17(5):1056–1061. [PubMed: 19165166]
16. Yoon DY, Moon JH, Kim HK, et al. Comparison of low-dose CT and MR for measurement of intra-abdominal adipose tissue: a phantom and human study. *Acad Radiol*. 2008; 15(1):62–70. [PubMed: 18078908]
17. Al-Attar SA, Pollex RL, Robinson JF, et al. Semi-automated segmentation and quantification of adipose tissue in calf and thigh by MRI: a preliminary study in patients with monogenic metabolic syndrome. *BMC Med Imaging*. 2006; 6:11. [PubMed: 16945131]
18. Hu HH, Nayak KS, Goran MI. Assessment of abdominal adipose tissue and organ fat content by magnetic resonance imaging. *Obes Rev*. 2011; 12(5):e504–e515. [PubMed: 21348916]
19. Liou TH, Chan WP, Pan LC, Lin PW, Chou P, Chen CH. Fully automated large-scale assessment of visceral and subcutaneous abdominal adipose tissue by magnetic resonance imaging. *Int J Obes (Lond)*. 2006; 30(5):844–852. [PubMed: 16418756]
20. Machann J, Thamer C, Stefan N, et al. Follow-up whole-body assessment of adipose tissue compartments during a lifestyle intervention in a large cohort at increased risk for type 2 diabetes. *Radiology*. 2010; 257(2):353–363. [PubMed: 20713612]
21. Peng Q, McColl RW, Ding Y, Wang J, Chia JM, Weatherall PT. Automated method for accurate abdominal fat quantification on water-saturated magnetic resonance images. *J Magn Reson Imaging*. 2007; 26(3):738–746. [PubMed: 17729369]
22. Zhou A, Murillo H, Peng Q. Novel segmentation method for abdominal fat quantification by MRI. *J Magn Reson Imaging*. 2011; 34(4):852–860. [PubMed: 21769972]
23. Reeder SB, Wen Z, Yu H, et al. Multicoil Dixon chemical species separation with an iterative least-squares estimation method. *Magn Reson Med*. 2004; 51(1):35–45. [PubMed: 14705043]
24. Reeder SB, McKenzie CA, Pineda AR, et al. Water-fat separation with IDEAL gradient-echo imaging. *J Magn Reson Imaging*. 2007; 25(3):644–652. [PubMed: 17326087]
25. Dixon WT. Simple proton spectroscopic imaging. *Radiology*. 1984; 153(1):189–194. [PubMed: 6089263]
26. Glover GH. Multipoint Dixon technique for water and fat proton and susceptibility imaging. *J Magn Reson Imaging*. 1991; 1(5):521–530. [PubMed: 1790376]
27. Glover GH, Schneider E. Three-point Dixon technique for true water/fat decomposition with B0 inhomogeneity correction. *Magn Reson Med*. 1991; 18(2):371–383. [PubMed: 2046518]
28. Alabousi A, Al-Attar S, Joy TR, Hegele RA, McKenzie CA. Evaluation of adipose tissue volume quantification with IDEAL fat-water separation. *J Magn Reson Imaging*. 2011; 34(2):474–479. [PubMed: 21780238]
29. Bley TA, Wieben O, Francois CJ, Brittain JH, Reeder SB. Fat and water magnetic resonance imaging. *J Magn Reson Imaging*. 2010; 31(1):4–18. [PubMed: 20027567]

30. Bornert P, Keupp J, Eggers H, Aldefeld B. Whole-body 3D water/fat resolved continuously moving table imaging. *J Magn Reson Imaging*. 2007; 25(3):660–665. [PubMed: 17326078]
31. Liu CY, McKenzie CA, Yu H, Brittain JH, Reeder SB. Fat quantification with IDEAL gradient echo imaging: correction of bias from T(1) and noise. *Magn Reson Med*. 2007; 58(2):354–364. [PubMed: 17654578]
32. Kim H, Taksali SE, Dufour S, et al. Comparative MR study of hepatic fat quantification using single-voxel proton spectroscopy, two-point dixon and three-point IDEAL. *Magn Reson Med*. 2008; 59(3):521–527. [PubMed: 18306404]
33. Hu HH, Kim HW, Nayak KS, Goran MI. Comparison of fat-water MRI and single-voxel MRS in the assessment of hepatic and pancreatic fat fractions in humans. *Obesity (Silver Spring)*. 2010; 18(4):841–847. [PubMed: 19834463]
34. Kullberg J, Ahlstrom H, Johansson L, Frimmel H. Automated and reproducible segmentation of visceral and subcutaneous adipose tissue from abdominal MRI. *Int J Obes (Lond)*. 2007; 31(12):1806–1817. [PubMed: 17593903]
35. Kullberg J, Johansson L, Ahlstrom H, et al. Automated assessment of whole-body adipose tissue depots from continuously moving bed MRI: a feasibility study. *J Magn Reson Imaging*. 2009; 30(1):185–193. [PubMed: 19557740]
36. Kullberg J, Karlsson AK, Stokland E, Svensson PA, Dahlgren J. Adipose tissue distribution in children: automated quantification using water and fat MRI. *J Magn Reson Imaging*. 2010; 32(1):204–210. [PubMed: 20575078]
37. Yu H, McKenzie CA, Shimakawa A, et al. Multiecho reconstruction for simultaneous water-fat decomposition and T2* estimation. *J Magn Reson Imaging*. 2007; 26(4):1153–1161. [PubMed: 17896369]
38. Bydder M, Yokoo T, Hamilton G, et al. Relaxation effects in the quantification of fat using gradient echo imaging. *Magn Reson Imaging*. 2008; 26(3):347–359. [PubMed: 18093781]
39. Reeder SB, Robson PM, Yu H, et al. Quantification of hepatic steatosis with MRI: the effects of accurate fat spectral modeling. *J Magn Reson Imaging*. 2009; 29(6):1332–1339. [PubMed: 19472390]
40. Yu H, Shimakawa A, McKenzie CA, Brodsky E, Brittain JH, Reeder SB. Multiecho water-fat separation and simultaneous R2* estimation with multifrequency fat spectrum modeling. *Magn Reson Med*. 2008; 60(5):1122–1134. [PubMed: 18956464]
41. Yu H, Shimakawa A, Reeder SB, McKenzie CA, Brittain JH. Magnitude fitting following phase sensitive water-fat separation to remove effects of phase errors. *Proc Intl Soc Magn Reson Med*. 2009; 17:461.
42. Yokoo T, Bydder M, Hamilton G, et al. Nonalcoholic fatty liver disease: diagnostic and fat-grading accuracy of low-flip-angle multiecho gradient-recalled-echo MR imaging at 1.5 T. *Radiology*. 2009; 251(1):67–76. [PubMed: 19221054]
43. Hernando D, Kellman P, Haldar JP, Liang ZP. Robust water/fat separation in the presence of large field inhomogeneities using a graph cut algorithm. *Magn Reson Med*. 2010; 63(1):79–90. [PubMed: 19859956]
44. Lloyd S. Least Squares Quantization in PCM. *IEEE Trans Info Theory*. 1982; 28:129–137.
45. Mei Z, Grummer-Strawn L, Pietrobelli A, Goulding A, Goran M, Dietz WH. Validity of body mass index compared with other body-composition screening indexes for the assessment of body fatness in children and adolescents. *American Journal of Clinical Nutrition*. 2002; 75:797–7985.
46. Brau AC, Beatty PJ, Skare S, Bammer R. Comparison of reconstruction accuracy and efficiency among autocalibrating data-driven parallel imaging methods. *Magn Reson Med*. 2008; 59(2):382–395. [PubMed: 18228603]
47. Yu H, Reeder SB, Shimakawa A, Brittain JH, Pelc NJ. Field map estimation with a region growing scheme for iterative 3-point water-fat decomposition. *Magn Reson Med*. 2005; 54(4):1032–1039. [PubMed: 16142718]
48. Maitra R. Initializing Partition-Optimization Algorithms. *IEEE Transactions on Computational Biology and Bioinformatics*. 2009; 6(1):144–157. [PubMed: 19179708]

49. Positano V, Gastaldelli A, Sironi AM, Santarelli MF, Lombardi M, Landini L. An accurate and robust method for unsupervised assessment of abdominal fat by MRI. *J Magn Reson Imaging*. 2004; 20(4):684–689. [PubMed: 15390229]

Figure 1.

Raw fat-fraction maps (left) and binary fat masks (right) for oil phantoms of varying volume and surface area complexity. The fat-fraction values are nearly unity in oil and nearly zero in agar and the signal void regions of air and glass.

Figure 2. Sample fat-only images from normal subject in (a) acquired sagittal view as well as (b) coronal and (c) axial reformats. The data was nearly isotropic and had high fat-water separation quality over the entire acquisition volume of interest, from top of liver dome to bottom of pelvic floor.

Figure 3.

The raw fat-fraction image in (a) suffers from noise and artifacts in the background and air cavities, and shows fat-fraction values for adipose and non-adipose tissues alike. Using an automated least-squares clustering algorithm, a masked fat-fraction image (b) is obtained, with noise removed from the image background and internal air-cavities. Finally, after determination of the physiologically-based maximum fat-fraction value η_{MAX} for adipose tissue, fat-fraction values below the threshold of $\eta_{MAX}/2$ are removed to create a binary adipose tissue map or “fat mask” as in (c). The acquired fat-only image is also shown in (d) for comparison.

Figure 4.

Validation of atMRI-based segmentation of VAT (a) with manual segmentation using SliceOMatic (b). Using atMRI, the VAT is isolated by simply drawing a contour (yellow line) on the fat mask, whereas with SliceOMatic the VAT must be isolated manually (yellow region). Examples of the most inferior (top) and superior (bottom) slices are shown, as chosen by the criteria described in the Methods section.

Figure 5.

Scatter plots comparing measurements of oil volume in the TAT phantom, for (a) three bottles of pure oil, (b) three bottles of pure oil with agar spheres, and (c) three bottles of pure oil with agar spheres and glass rods. A fourth plot (d) combines all data points from all nine bottles. Fit parameters for linear regression are summarized in Table 1.

Figure 6.

Scatter plots comparing measurements using atMRI with manual validation, for (a) automated TAT and (b) semi-automated VAT using atMRI in normal adult subjects, and (c) automated TAT and (d) semi-automated VAT in overweight adolescent females. Fit parameters for linear regression are summarized in Table 1.

* Indicates statistical significance

Figure 7.

Box-and-whisker plots illustrate anthropometric and atMRI-derived measure comparisons between normal adult subjects and adolescent overweight females. The boxes are mean $\pm$ standard deviation across the group, and whiskers are minimum and maximum value. P-values are from Student's t-test between groups, with an asterisk denoting statistical significance. Note that BMI was a selection criterion for the overweight group.

Table 1

Linear Regression Results for Total and Visceral Adipose Tissue Volume Measurements

	r^2	slope	intercept
Phantom : Oil bottles	0.991	0.923 ± 0.087	44 ± 47 cc
Phantom : Oil, Agar bottles	0.995	0.923 ± 0.064	25 ± 35 cc
Phantom : Oil, Agar, Void bottles	0.995	0.959 ± 0.065	18 ± 35 cc
Phantom : All bottles	0.992	0.935 ± 0.032	29 ± 17 cc
Adult normal TAT	0.991	0.994 ± 0.026	-808 ± 190 cc
Adult normal VAT	0.963	1.036 ± 0.057	-270 ± 93 cc
Adolescent overweight female TAT	0.987	1.028 ± 0.042	-402 ± 386 cc
Adolescent over weight female VAT	0.985	1.287 ± 0.056	-370 ± 68 cc

Table 2

Comparison of VAT Segmentation Time

	Adult normal subjects		Adolescent overweight females		All subjects	
	Manual	Semi-automatic	Manual	Semi-automatic	Manual	Semi-automatic
Minimum/maximum (min / study)	120 / 300	15 / 60	90 / 300	25 / 40	90 / 300	15 / 60
Average (min / study)	230.0 $\pm$ 58.6	27.7 $\pm$ 13.2	195.0 $\pm$ 88.6	34.0 $\pm$ 5.2	216.0 $\pm$ 72.5	30.2 $\pm$ 11.0
Minimum/maximum (sec / slice)	51 / 154	7 / 27	47 / 120	11 / 22	47 / 154	7 / 27
Average (sec / slice)	107.0 $\pm$ 27.1	12.8 $\pm$ 5.6	86.8 $\pm$ 32.6	15.8 $\pm$ 3.0	98.9 $\pm$ 30.5	14.0 $\pm$ 4.9