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MRI based validation of abdominal adipose tissue measurements from DXA in postmenopausal women

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Abstract

Introduction: Visceral adipose tissue (VAT) is a hypothesized driver of chronic disease. Dual-energy X-ray absorptiometry (DXA) potentially offers a lower cost and more available alternative compared to gold-standard magnetic resonance imaging (MRI) for quantification of abdominal fat sub-compartments, VAT and subcutaneous adipose tissue (SAT). We sought to validate VAT and SAT area (cm^2) from historical DXA scans against MRI.

Methodology: Participants (n=69) from the Women's Health Initiative (WHI) completed a 3 T MRI scan and a whole body DXA scan (Hologic QDR2000 or QDR4500; 2004–2005). A subset of 43 participants were scanned on both DXA devices. DXA-derived VAT and SAT at the 4th lumbar vertebrae (5 cm wide) were analyzed using APEX software (v4.0, Hologic, Inc., Marlborough, MA). MRI VAT and SAT areas for the corresponding DXA region of interest were quantified using sliceOmatic software (v5.0, Tomovision, Magog, Canada). Pearson correlations between MRI and DXA-derived VAT and SAT were computed, and a Bland-Altman analysis was performed.

Results: Participants were primarily non-Hispanic white (86%) with a mean age of 70.51 ± 5.79 years and a mean BMI of 27.33 ± 5.40 kg/m^2. Correlations between MRI and DXA measured VAT and SAT were 0.90 and 0.92, respectively ($p \leq 0.001$). Bland-Altman plots showed that DXA-VAT slightly overestimated VAT on the QDR4500 (−3.31 cm^2); this bias was greater in the smaller subset measured on the older DXA model (QDR2000; −30.71 cm^2). The overestimation of DXA-SAT was large (−85.16 to −118.66 cm^2), but differences were relatively uniform for the QDR4500.

Conclusions: New software applied to historic Hologic DXA scans provide estimates of VAT and SAT that are well-correlated with criterion MRI among postmenopausal women.

Keywords

Dual-energy X-ray absorptiometry; body composition; visceral fat; subcutaneous fat; validation; magnetic resonance imaging

INTRODUCTION

Anthropometric measurements of BMI and waist circumference (WC), proxies of obesity and fat distribution, have proven to be useful for the study of health risks related to excess adiposity.[1–3] However, a growing body of evidence demonstrates that the distribution and type of adipose tissue, [i.e. visceral adipose tissue (VAT) versus subcutaneous adipose tissue (SAT) in the abdomen] are better prognostic indicators of health than BMI or WC or directly measured total body fat, therefore of interest for incorporation into large epidemiologic studies.[2,4]

The SAT compartment is a non-ectopic fat depot, [2,3] while VAT is an ectopic depot within the envelope formed by the abdominal muscles and in mesenteric fat.[2,3] Thus, VAT surrounds organs and blood vessels. VAT and SAT differ in their structural composition,

metabolic activity, and function, with respect to glucose and lipid metabolism, insulin sensitivity and inflammation.[5] A small body of human cross-sectional studies and clinical trials provide evidence that VAT may be a more important driver of health risks related to obesity than other depots, due to higher metabolic and inflammatory activity.[2,4] A more powerful, affordable, and accessible tool to enable large-scale studies about the associations between various fat depots and health risks is lacking.

Two gold-standard imaging methods – computed tomography (CT) and magnetic resonance imaging (MRI) imaging - are cost prohibitive for use in large epidemiologic cohorts, involve a number of prevalent exclusion criteria, and can involve exposure to radiation (CT only);[6] therefore, these imaging modalities are impractical in the clinic and for large-scale research studies.

Recently developed software for dual-energy X-ray absorptiometry scans (DXA) scans (APEX, Hologic Inc., Marlborough, MA) is a means by which the VAT and SAT sub-compartments of abdominal adipose can be quantified on historical DXAs. Older longitudinal cohorts were previously limited to total body and trunk fat estimates. While modern DXA models such at the GE Lunar Prodigy and iDXA (GE/Lunar Radiation Corp, Madison, WI), and the Hologic Discovery and Horizon series (Marlborough, Massachusetts) provide VAT and SAT measures in adults and have been validated by CT and MRI across many populations,[7–13] they have not existed long enough to have accumulated long-term adjudicated health outcomes. Well-characterized national cohorts, such as the Women's Health Initiative (WHI), which have available repeat DXA scans on 11,020 postmenopausal women, are particularly appealing for the large-scale estimation and study of VAT and SAT depots and risk of a variety of adjudicated incident cardiovascular, cancer, and bone health outcomes over more than 25 years follow-up.

The present study uses criterion MRI to validate DXA-derived VAT and SAT measured with the new DXA software for both the Hologic QDR4500 model and the older QDR2000 model. We hypothesize that abdominal VAT and SAT estimates from both DXA models are highly correlated with corresponding MRI measures. If sufficiently validated, these new measures of VAT and SAT will allow us to apply the new software in the full WHI DXA cohort and examine multiple health outcomes related to the new and specific estimates of VAT and SAT.

METHODS

Study Population

Postmenopausal women aged between 50–79 years were enrolled in the WHI clinical trials and observational study between 1993 and 1998 at 40 clinical centers across the U.S. (n=161,808). A subcohort consented to complete body composition measurements via DXA at three WHI clinical centers in Pittsburgh, PA; Birmingham, AL; and Tucson/Phoenix, AZ (n=11,020). Among those who consented to body composition measurements at the Tucson/Phoenix, AZ site, a convenience sample agreed to undergo an MRI scan (n=69) concurrent with their planned follow-up DXA measures between 2004 and 2005. The DXA machines included two models, the Hologic QDR2000 or QDR4500w. Of the 69 tested,

43 were scanned on both DXA devices. The mean number of days between MRI and DXA and between each DXA scan on the two different scanners were 15.18±9.25 and 17.51±10.33, respectively. Age and race/ethnicity were previously ascertained by self-report questionnaire at WHI baseline. The protocol and consent forms were approved by the institutional review board and all participants provided written informed consent. Study design and participant characteristics for the WHI and WHI DXA subcohort have been described in detail elsewhere.[14]

Anthropometry

Weight and height were measured in the clinic on a balance-beam scale to the nearest 0.1 kg and wall-mounted stadiometer to the nearest 0.1 cm, respectively,[15,16] according to standard WHI protocol. BMI was calculated as weight (kg)/height $(m)^2$. Waist circumference to the nearest 0.5 cm was measured at the narrowest part of the waist over non-binding undergarments. The anthropometry measurements were completed during the MRI scan visit and occurred within six weeks from the DXA scan visit.

DXA body composition measurements

Whole-body DXA (QDR2000 and 4500W; Hologic Inc., Marlborough, MA) scans were used to determine both regional and total body composition, as previously published. In brief, measurements included areal bone mineral density (aBMD; g/cm^2), lean soft tissue mass (kg), and fat mass (kg). The scan measurements were conducted following standardized procedures for a whole body scan. Participants were measured wearing only gowns to eliminate possible artifacts due to clothing and fasteners. The participant was positioned in the center of the scanning table with her head just below the head of the table. The arms were lying along the sides of the body, with separation between the body and arms and hands placed palm down. Once completed, the whole body DXA scans were analyzed for the manufacturer defined regions of interest (ROI) following the standard analysis protocol in the Hologic User Manual, using the Hologic whole body and sub-region analysis modes (QDR System software ver. 12.1).[14,17,18] Trunk fat includes all fat in a region defined by an upper border immediately inferior to the chin, an inferior border immediately superior to the iliac crest, and lateral boundaries that bisect the arm socket and positioned as close to the body as possible without including hands and arms. The WHI DXA quality assurance program included standard WHI protocols for positioning and analysis of DXA scans by technicians certified by Hologic and the WHI Bone Density Coordinating Center; local daily and weekly phantom scans; circulating Hologic spine, hip, and block calibration phantoms scanned by each site and instrument; and machine and technician performance monitoring by review of phantom scans, random sampling, and review of scans with specific problems.[14,17]

To estimate abdominal VAT and SAT, the DXA images were re-analyzed using new software (Hologic APEX 4.0 software toolbox). The procedures outlined in the Hologic Operator Manual[18] were used to estimate VAT and SAT in an abdominal region of interest (ROI) 5 cm wide at approximately the 4th lumbar vertebrae, taking care to avoid the iliac crest and limit bony interference with the soft tissue measures (Figure 1). Total abdominal fat for the new ROI was measured by DXA based on the standard principles of DXA.[19] To estimate VAT

and SAT in the ROI, the following sections within the abdominal "slice" were separated by lines of demarcation: the total abdominal area (area between each outer edge of the soft tissue on both sides of the patient), inner abdominal wall area (inner edge to outer edge of the abdominal muscle on each side of the body), and the visceral cavity area. Although the ROIs are automatically "boxed" on the screen by the software, proper alignment of the ROI and lines of demarcation horizontally were achieved on each scan by manual adjustment of the selection boxes by trained technicians using the Hologic APEX 4.0 software toolbox. If the vertical borders were incorrectly placed below the iliac crests, capturing bone, the scans were excluded per APEX software manual instructions.[18] The proprietary Hologic algorithms generated the values for visceral and subcutaneous adipose tissue area (cm^2) based on the lines of demarcation and using the following steps.[12] Lateral subcutaneous fat demarcated in the image on each side of the abdominal cavity was measured by DXA and used to model the anterior/posterior amount of subcutaneous fat over the visceral cavity. The software then added the estimate of the SAT overlying the visceral cavity to the measured lateral SAT for a total abdominal SAT value for the ROI. This total abdominal SAT was subtracted, by the software, from the total abdominal fat measured by DXA to give the estimated DXA-VAT.[12]

Following a training set of 173 DXA scans, two master DXA technicians used the standardized procedures laid out in the Hologic Operator Manual, to select the abdominal ROI on the total body scans for computation of VAT and SAT across the full set of DXA scans. Each technician repeated the selection of the ROIs on all DXA scans in the subset. The repeat ROI selection and analyses were performed on a different day; no data from the first ROI selection and analyses was available during the repeat ROI selection and analyses to prevent bias. The inter-rater and intra-rater precision were evaluated for selection of abdominal ROIs on each DXA scan and recorded for quality assurance.

MRI body composition measurements

Whole body scans were conducted using a T1 weighted sequence on a the 3-T MRI scanner (model Genesis Signa, General Electric) platform at the University of Arizona Medical Center, as previously published.[14] Scans were acquired using a 256 × 256 matrix, voxel size = 1.875×1.875×10mm, and resolution of 0.5333 pixels per mm. Participants (n=69) were placed in the scanner with arms extended above the head and were scanned for the lower body first and then the upper body. The upper body imaging, relevant to this investigation, was obtained using a scout view to identify the ischial tuberosity; the scan then proceeded from the ischial tuberosity to the fingertips resting above the head. The MRI average slice thickness was 10mm, with a 40mm inter-slice gap.

Two trained technicians completed MRI soft tissue analyses using sliceOmatic image analysis software (Tomovision, Magog, Canada). A multiple-step procedure was used to segment images into the specific tissue compartments, according to standardized procedures from the software manufacturer (Figure 1).[20] Thresholds were determined manually to distinguish adipose from lean tissues. The technician further delineated the adipose tissue into VAT and SAT using previously described anatomical definitions,[21] where VAT was the adipose tissue inside the inner border of the abdominal wall less intermuscular and

paravertebral adipose, and SAT the adipose outside the outer border of the abdominal wall. VAT and SAT tissue areas (cm^2) were then quantified automatically. The single MRI slice immediately superior to the iliac crest, the slice most proximal to the new DXA VAT ROI, was used in this analysis. Each technician reanalyzed MRI scans (n=10) over a week after original analysis to perform intra-rater precision analysis and technician 2 analyzed MRI scans (n=10) originally analyzed by technician 1 to assess inter-rater precision.

Statistical Analysis

Descriptive analyses were conducted on demographic and body composition assessments. Scatter plots were used to illustrate the distribution and association of body composition measurements for MRI and DXA scans from both DXA models. Pearson correlation coefficients were estimated between MRI and DXA measurements on both DXA models. Limits of agreement between MRI-VAT and DXA-VAT, as well as MRI-SAT and DXA-SAT, were assessed using the Bland and Altman technique. Statistical analyses were conducted using 2-tailed tests of significance using an alpha of 0.05 (STATA version 16.1).

RESULTS

The inter and intra-rater precision for DXA and MRI analyses were high. For DXA, the lowest intraclass correlation coefficient (ICC) was 0.98 for the VAT compartment on the QDR4500 within rater and the highest ICC was 1.0 for the SAT compartment on the QDR2000 within rater (Supplemental Table 1). For MRI, the inter-rater ICC ranged from 0.99 to 1.0 across regions of interest and sub-compartments, while the intra-rater ICC ranged from 0.99 to 1.0 (Supplemental Table 2).

In the study sample of predominantly white, Non-Hispanic women (86%), participants on average were 70.5 ± 5.8 years of age with a BMI of 27.3 ± 5.4 kg/m^2 and 26.9 ± 9.3 kg of total body fat at the time of the MRI scans. SAT area was greater than VAT area among participants. DXA-SAT was estimated at 330.7 ± 121.3 cm^2 and MRI-SAT at 245.5 ± 117.2 cm^2. DXA-VAT was estimated at 129.9 ± 64.3 cm^2 and MRI-VAT was 126.6 ± 64.5 cm^2 in the full sample. (Table 1). Characteristics for WHI DXA cohort participants in Arizona at baseline compared to women in the MRI subset at WHI baseline are provided in Supplemental Table 3.

The VAT and SAT correlations between DXA and MRI for the larger sample measured on the QDR4500 (n=69) are presented in Table 2. The correlation between DXA-VAT and MRI-VAT was 0.90, $p \leq 0.001$. The correlation between DXA-SAT and MRI-SAT was 0.92, $p \leq 0.001$. Similar correlations with MRI were observed in a head-to-head comparison of DXA models among women measured on all three devices (n=43, $p \leq 0.001$; Supplemental Table 4).

Limits of agreement between abdominal MRI-VAT (panel A) and SAT (panel B) and DXA-VAT and SAT, respectively, are demonstrated in the Bland-Altman plots (Figure 2). The mean difference between MRI and DXA measures of VAT by DXA QDR2000 and QDR4500 was −30.71 and −3.31 cm^2, respectively. The mean difference between MRI and DXA measures of SAT by the DXA QDR2000 and QDR4500 compared to MRI was

−118.66 and −85.16 cm^2, respectively. The slopes visualized in the Bland-Altman plots indicated that the observed differences were uniform versus appearing at the extremes of high and low adiposity for the QDR4500, but not for the QDR2000.

Regression equations for QDR2000 and QDR4500 VAT were VAT= 15.30 + 1.12(MRI VAT) and VAT= 16.12 + 0.90(MRI VAT), respectively. The regression equations for QDR2000 and QDR4500 SAT were SAT= 99.23 + 1.08(MRI SAT) and SAT= 96.61+ 0.95(MRI SAT), respectively.

DISCUSSION

As hypothesized, abdominal VAT and SAT estimates from DXA were highly correlated with the corresponding MRI derived soft-tissue measure. Inter- and intra-rater precision was not appreciably different across DXA models, nor were the correlations with criterion MRI. Further, the correlations between DXA VAT and SAT presented are consistent with published correlations from other studies utilizing CT or MRI derived measures of the corresponding tissues (e.g. 0.82–0.93).[8,12,22–24] Thus, these DXA derived VAT and SAT values from older DXA models, despite poorer image quality in comparison to modern technology, are reproducible and highly correlated with criterion MRI.

Nevertheless, there were some differences between Hologic models and tissue depots. The VAT measures, especially for the QDR4500 were well aligned with the MRI, but the SAT measures were somewhat overestimated across the two DXA models. Given the low accessibility of MRI and CT, especially in the prevention setting, and the good agreement between DXA and MRI, DXA derived values can be reasonably used in large epidemiologic studies to estimate VAT, which can help develop a profile of those at greatest risk for adverse health events.

Though several studies have examined the correlation between criterion CT- or MRI-derived VAT and SAT and DXA derived abdominal fat, trunk fat, or total body fat beginning in the 1990s,[25–31] these studies are insufficient to determine if DXA-derived VAT is a valid measure of criterion VAT, and similarly if DXA-derived SAT is a valid measure of criterion SAT. Given the differences in metabolic and inflammatory activity between abdominal adipose sub-compartments,[2,4,32–36] specifically measuring VAT and SAT rather than total abdominal or trunk fat, as proxies for visceral deposition, is important and requires validated imaging methods. Several studies have validated DXA-VAT and SAT from modern DXA models, such as GE Lunar iDXA and Hologic Discovery,[7–13] which are valuable, yet, lack the long-term follow-up for the prediction of major health outcome such as cardiovascular disease, cancer, and mortality. Using new software, the present study enables the utilization of older DXA scan estimates of VAT and SAT for application in studies with long-term adjudicated outcomes, such as WHI. In addition, to our knowledge, this is the first validation of DXA-derived VAT and SAT specifically among postmenopausal women.

Similar to other studies, [7,11,37] our study among postmenopausal women demonstrated some bias towards overestimation of abdominal adipose depots by DXA, particularly for SAT and when using the older Hologic QDR2000 to derive VAT and SAT estimates from

APEX software. The differences were relatively uniform across the spectrum of adipose levels without increasing over- or under-estimation at the tails for the QDR4500, but not for the QDR2000 where adipose may be underestimated among postmenopausal women with the greatest adipose and overestimated among postmenopausal women with lowest adipose. Meanwhile, others have found underestimation of abdominal adipose tissue depots in certain populations. For example, DXA underestimated VAT compared to MRI or CT among older men with diabetes [8] and females with polycystic ovarian syndrome.[24] Among HIV patients, the underestimation of VAT progressively increased with greater VAT.[38] In one of the largest male and female populations to date (N=1477 females and 1212 males), using a more modern Hologic Discover W DXA scanner, there was some regression toward the mean, with underestimation of VAT compared with MRI occurred at lower VAT levels, while overestimation occurred at higher VAT levels.[13] Therefore, it is important to understand the selected DXA model relationship to the criterion method in the same or a similar population to be used in future studies. In addition, though the correlations between DXA VAT and SAT estimates and MRI VAT and SAT are strong, the minimal clinically important difference needs to be established for VAT in relation to health risks to understand if the bias of any given DXA model outweighs the benefits of its use.

The validation of DXA-VAT and DXA-SAT among postmenopausal women is particularly meaningful because millions of postmenopausal women are scanned by DXA in U.S. clinics and hospitals annually to meet osteoporosis screening guidelines.[39] The guidelines recommended bone mineral density (BMD) assessment by DXA for all women ≥65 years of age, and younger postmenopausal women with risk factors for osteoporosis and fractures.[40] Newer DXA machines, commonly available in clinics, have the ability to estimate VAT and SAT at the point of care. However, soft-tissue software packages and phantoms for calibration are seldom purchased and the total body scans required to estimate VAT and SAT are not routinely performed and clinical scans tend to be limited to BMD at the most common fracture sites of hip and spine.[40] Though it remains to be seen whether VAT and SAT will be superior to WC and BMI for identifying high-risk individuals for intervention, now, using the APEX software to reassess historic DXA scans, there is a tool to perform these analyses in large cohorts with sufficient follow-up and adjudicated events that were previously limited to anthropometry and abdominal or total fat. If VAT by DXA proves to outperform anthropometric and total fat measures for segregating those at risk for CVD, diabetes, and/or cancers in these readily available datasets, then its clinical utility may outweigh short comings in terms of its relation to criterion methods and DXA measures may be formally tested prospectively with newer DXA models and software. There may also be greater impetus for clinics and researchers to purchase and utilize the necessary software for soft-tissue components of DXA and perform the rapid total body scans required to estimate VAT and SAT (<5 minutes), particularly among postmenopausal women.

Strengths and Limitations

The ability to compare across two DXA models within the same study and versus criterion MRI is a major strength of the study. Standardized protocols for image analysis within scan type allowed for minimal intra- and inter-rater variability. However, differences in standard arm positioning for DXA versus MRI and variance in torso length may have contributed,

in part, to differences in VAT and SAT measures across technologies. Generalizability of the analysis is limited by the lack of diversity among the postmenopausal sample, therefore correlations between MRI and DXA-derived estimates of VAT and SAT from younger women, women of different race or ethnic backgrounds and men may vary. Differences in abdominal VAT by racial/ethnic group have been noted by others.[41,42] Thus, the validation of DXA-derived abdominal fat depots requires replication in more diverse populations.

CONCLUSION

Abdominal VAT and SAT estimates from Hologic QDR2000 and QDR4500 DXA scans were highly correlated with corresponding gold standard MRI soft-tissue measures. Despite apparent overestimation of SAT in this small subset, the need to better understand the more inflammatory and metabolically active VAT associations with key clinical outcomes supports the use of this new DXA software in large historic epidemiologic studies to test these associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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For a list of all the investigators who have contributed to WHI science, please visit: https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf

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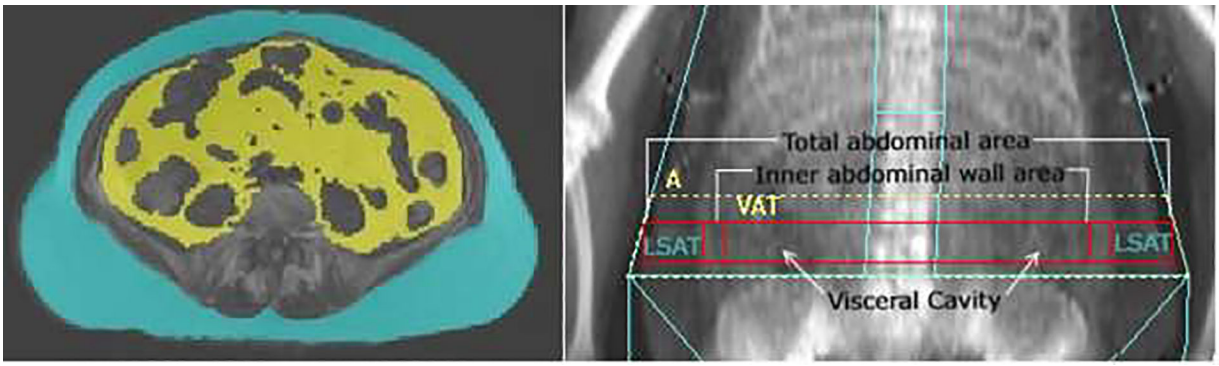

Figure 1.

Representative example of abdominal visceral and subcutaneous fat quantification by MRI and DXA techniques.

The MRI image (left) represents an axial slice at the L3-L4 intervertebral space; slice thickness is 10mm. The visceral adipose tissue (VAT) is colored in *yellow* and subcutaneous adipose tissue is colored in *teal blue*. The two-dimensional DXA (right) region of interest is demarcated by the red lines drawn at L4. The APEX software measures the visible lateral subcutaneous adipose tissue (LSAT) on the right and left sides from the medial edge of the LSAT to the lateral edge of LSAT (boxed in red). The measured LSAT is used to model the anterior-posterior (AP) subcutaneous adipose over the visceral cavity based on a proprietary formula. The software then adds the estimate of the SAT overlying the visceral cavity to the measured LSAT for a total abdominal SAT value for the ROI. This total abdominal SAT is subtracted, by the software, from the total abdominal fat measured by DXA to estimate DXA-visceral adipose tissue. A, android subregion

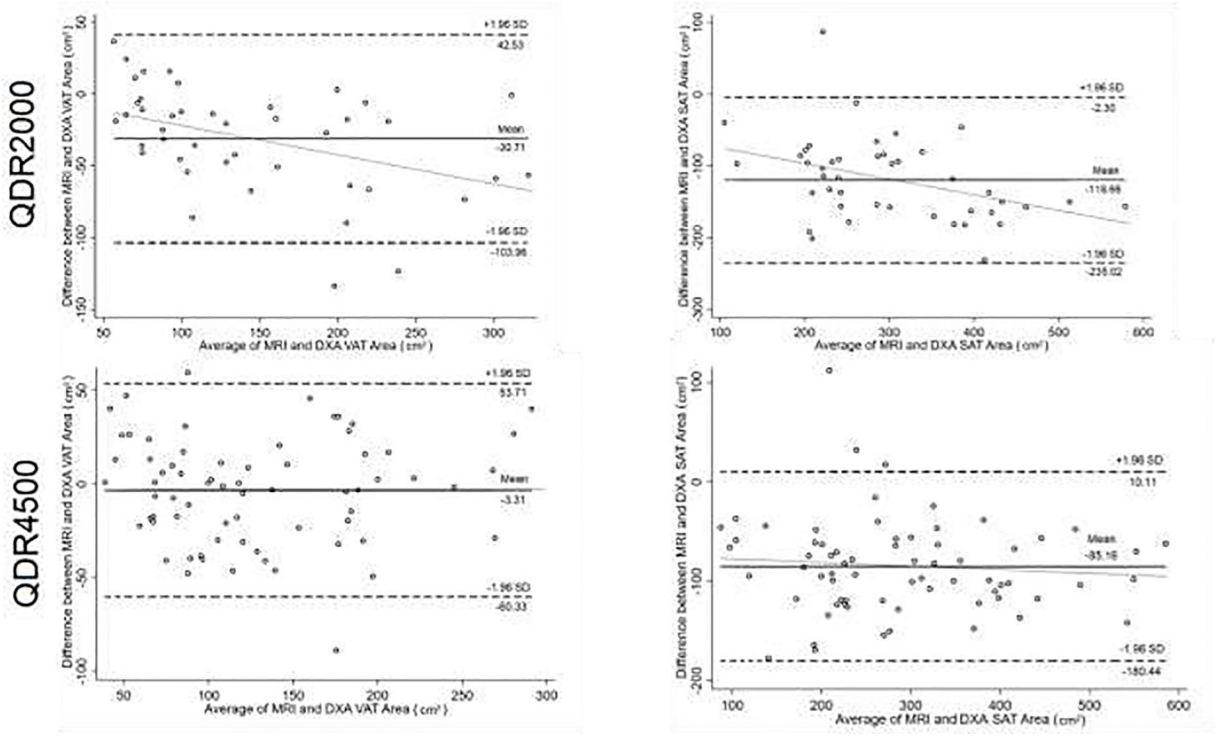

Figure 2.

Bland-Altman plot of MRI-DXA visceral (VAT, panel A) and subcutaneous (SAT, panel B) adipose tissue difference versus average of MRI and DXA for a single abdominal slice (QDR2000: n=43 and QDR4500: n=69)

Table 1:

Body composition characteristics of the WHI DXA cohort at the 2004–2005 clinic visit for those with concurrent MRIs

	Full Sample (N=69)		Subset (n=43)[a]		
Variable, Mean ± SD (Median, IQR) (skewness & kurtosis)	**MRI**	**QDR4500 DXA**	**MRI**	**QDR2000 DXA**	**QDR4500 DXA**
Total body fat (kg)		26.9 ± 9.3 (26.6, 13.7) (0.4 & 2.8)		30.3 ± 10.3 (26.3, 10.1) (0.5 & 2.9)	26.7 ± 8.4 (26.6, 13.7) (0.6 & 3.3)
Trunk fat (kg)		12.7 ± 5.3 (11.7, 8.1) (0.8 & 4.3)		13.9 ± 6.3 (12.4, 6.6) (0.8 & 3.6)	12.7 ± 5.2 (11.7, 8.4) (1.1 & 5.1)
VAT (cm^2)	126.6 ± 64.5 (107.9, 100.6) (0.9 & 3.1)	129.9 ± 64.3 (120.5, 92.6) (0.5 & 2.6)	128.9 ± 68.9 (104.8, 101.5) (1.0 & 3.1)	159.6 ± 85.0 (138.6, 128.3) (0.6 & 2.3)	134.7 ± 64.1 (117.6, 112.7) (0.6 & 2.4)
SAT (cm^2)	245.5 ± 117.2 (250.9, 152.3) (0.5 & 2.8)	330.7 ± 121.3 (311.9, 148.3) (0.5 & 2.8)	240.7 ± 95.2 (250.9, 133.9) (0.5 & 2.9)	359.4 ± 117.9 (334.8, 187.8) (0.4 & 2.7)	323.7 ± 104.4 (282.9, 139.7) (0.5 & 2.9)

[a]Subset of women scanned on all three devices

Table 2.

Pearson correlation coefficients between fat compartments for the DXA and MRI (n=69)[a]

MRI Variable	DXA-VAT (cm^2)	DXA-SAT (cm^2)
VAT single slice (cm^2)	0.90	0.69
SAT single slice (cm^2)	0.73	0.92

[a] $p \leq 0.001$; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue