

# Dual-Energy X-Ray Absorptiometry for Quantification of Visceral Fat

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Obesity is the major risk factor for metabolic syndrome and through it diabetes as well as cardiovascular disease. Visceral fat (VF) rather than subcutaneous fat (SF) is the major predictor of adverse events. Currently, the reference standard for measuring VF is abdominal X-ray computed tomography (CT) or magnetic resonance imaging (MRI), requiring highly used clinical equipment. Dual-energy X-ray absorptiometry (DXA) can accurately measure body composition with high-precision, low X-ray exposure, and short-scanning time. The purpose of this study was to validate a new fully automated method whereby abdominal VF can be measured by DXA. Furthermore, we explored the association between DXA-derived abdominal VF and several other indices for obesity: BMI, waist circumference, waist-to-hip ratio, and DXA-derived total abdominal fat (AF), and SF. We studied 124 adult men and women, aged 18–90 years, representing a wide range of BMI values (18.5–40 kg/m<sup>2</sup>) measured with both DXA and CT in a fasting state within a one hour interval. The coefficient of determination ( $r^2$ ) for regression of CT on DXA values was 0.959 for females, 0.949 for males, and 0.957 combined. The 95% confidence interval for  $r$  was 0.968 to 0.985 for the combined data. The 95% confidence interval for the mean of the differences between CT and DXA VF volume was –96.0 to –16.3 cm<sup>3</sup>. Bland–Altman bias was +67 cm<sup>3</sup> for females and +43 cm<sup>3</sup> for males. The 95% limits of agreement were –339 to +472 cm<sup>3</sup> for females and –379 to +465 cm<sup>3</sup> for males. Combined, the bias was +56 cm<sup>3</sup> with 95% limits of agreement of –355 to +468 cm<sup>3</sup>. The correlations between DXA-derived VF and BMI, waist circumference, waist-to-hip ratio, and DXA-derived AF and SF ranged from poor to modest. We conclude that DXA can measure abdominal VF precisely in both men and women. This simple noninvasive method with virtually no radiation can therefore be used to measure VF in individual patients and help define diabetes and cardiovascular risk.

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## INTRODUCTION

Obesity is the major risk factor for the metabolic syndrome and, through it, diabetes as well as cardiovascular disease. It is becoming clear that the distribution of body fat is more important in this regard than simply the amount of fat. For instance, android rather than gynoid distribution of fat is more often associated with the metabolic syndrome, diabetes, and cardiovascular disease (1–6). Therefore, anthropometric measurements such as the waist size and the waist-to-hip ratio have been shown in epidemiological studies to predict adverse outcomes (5,7,8).

More recently it has been demonstrated that even within abdominal fat (AF), it is visceral fat (VF) rather than subcutaneous fat (SF) that is the major predictor of adverse events (9–15). Currently, the most commonly used imaging technique for measuring VF is abdominal X-ray computed tomography (CT) (16–20). Although this technique has been well validated

it is not optimal as a screening tool for VF because of radiation dose, manual image analysis to separate SF and VF, and the need for access to heavily utilized clinical equipment. While magnetic resonance imaging (MRI), which has also been used for measurement of VF measurement (21,22), avoids the radiation exposure encountered with CT, analysis is still largely manual and time-consuming, and as with CT, requires heavily utilized clinical equipment.

Dual-energy X-ray absorptiometry (DXA) can accurately measure body composition with high-precision, low X-ray exposure, and short-scanning time (23–26). DXA subdivides soft tissue into lean and fat compartments in order to allow whole body and regional measurement of body composition. Earlier attempts at using DXA measured total AF and did not utilize algorithms that segment AF into VF and SF (27,28). As a result DXA-derived total AF was not found to offer an advantage over anthropometric measurements.

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Herein, we describe a newly developed fully automated method for segmenting AF into SF and VF within the android region using DXA that has been approved for clinical use by the US Food and Drug Administration. Using this approach we can measure total body fat, total AF, abdominal SF, and abdominal VF. We validated our newly developed method against CT in a patient population with a wide range of BMI. Furthermore, we explored the association between DXA-derived VF and BMI, waist circumference, waist-to-hip ratio, and DXA-derived AF and SF.

## METHODS AND PROCEDURES

### Patient population and protocol

The protocol was approved by the Institutional Review Board of the Oregon Health and Science University, Portland, OR, and all subjects provided written informed consent. The study population included 124 adult men and women volunteers, aged 18–90 years, recruited from a wide range of BMI values (18.5–40 kg/m<sup>2</sup>). For each subject, height, weight, and hip and waist circumferences were measured. They were then imaged with DXA and CT in a random order within a one hour interval in the fasting state.

### Sample size calculation

Sample size was calculated to reliably determine whether the correlation coefficient between DXA and CT exceeded a lower limit of  $r = 0.90$ . Using an internal engineering dataset, we conservatively estimated the correlations between DXA and CT VF volume for the study population as  $r = 0.961$  for males and  $r = 0.954$  for females. Calculating the power of a one-tailed test of the correlation against the value 0.90,  $\alpha = 0.05$ , applying Fisher's Z-transformation and using a power of 90% as a basis for calculating sample size, the results indicated that a sample consisting of 60 subjects of each gender would suffice if the true correlation were 0.95 or greater.

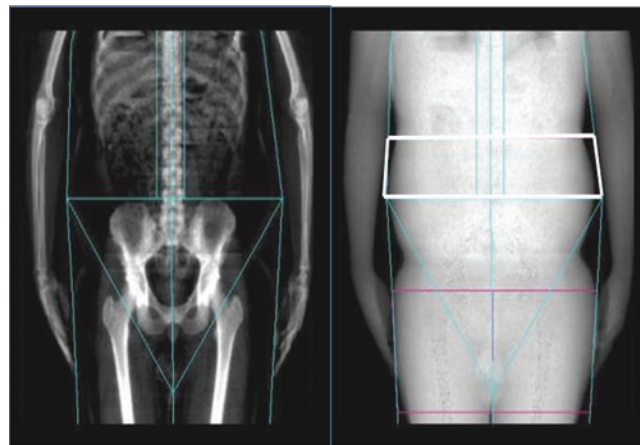
### DXA measurements

Total body imaging was acquired using the GE Healthcare Lunar iDXA and analyzed using enCORE software version 13.6. Daily quality control scans were acquired during the study period. No hardware or software changes were made during the course of the trial. Subjects were scanned using standard imaging and positioning protocols. For measuring android fat, a region-of-interest is automatically defined whose caudal limit is placed at the top of the iliac crest and its height is set to 20% of the distance from the top of the iliac crest to the base of the skull to define its cephalad limit (Figure 1). Abdominal SF and VF were estimated within the android region. Fat mass data from DXA was transformed into CT adipose tissue volume using a constant correction factor (0.94 g/cm<sup>3</sup>). This constant is generally consistent with the density of adipose tissue (29) and represents a value that was optimized in our training algorithm and not altered in the validation procedure.

### CT measurements

CT scans were acquired using a Philips iCT 256 scanner running Extended Brilliance Workspace software version 3.0.0. A noncontrast enhanced standard abdominal scan was performed using 120 kVp, and 5-mm slice thickness. Subjects were placed in the supine position with arms above their head. Contiguous cross-sectional abdominal images were captured over 150 mm of the abdomen, beginning at the top of S1 and moving towards the head.

CT images were segmented using a semiautomated method to remove the subcutaneous AF, and the remaining tissue volumes were reconstructed from DICOM images using the GE Healthcare Advantage Workstation (version 4.1). To account for differences in patient positioning and variation in attenuation across subjects, a subject-specific threshold in Hounsfield units was developed based



**Figure 1** Sample dual-energy X-ray absorptiometry (DXA) bone and tissue images. The straight lines defined by the skeletal image (left) represent automated DXA regions of interest. Base of android region is keyed off of top of the iliac crest, shown as the top of the pelvic triangle. The android region is highlighted with solid white line on DXA soft tissue image (right).

on manual selection of a region of high confidence VF in a single slice. The threshold was set for each patient at 2 s.d. from the mean VF Hounsfield value in the region-of-interest. This threshold was applied to all slices and the volume of VF was reported.

All CT data was analyzed by a single operator. Approximately 20% of the data (27 subjects) were randomly selected for verification of CT results by a second operator. The average difference in VF volume between the two testers was 3.3%. This agrees with previous reports in the literature showing 3% difference using similar methods (30,31).

### Data analysis

CT data were transferred to GE Global Research Center (Niskayuna, NY), and DXA data were transferred to GE Healthcare Lunar (Madison, WI). CT and DXA images were not shared between the two centers in order to minimize any potential bias in the algorithm development and validation process.

### Modeling of VF estimation

Prior to the start of the study, an internal engineering dataset was used to model the relationship between DXA estimated and CT measured VF volumes. Because the model relies on geometric assumptions of fat distribution in the abdomen, modeling parameters were optimized separately for females and males. For each sex, analysis of the clinical dataset consisted of two predefined phases. In the first phase, a small sample of the clinical dataset was identified that reflected population heterogeneity in several key areas including age, height, weight, and BMI. This subsample was used to estimate algorithm performance and ultimately was added to the internal engineering dataset to refine the DXA modeling parameters. In the second phase of analysis, validation was performed using the remaining dataset.

The android region contains both VF and SF. Generally, the SF forms a layer of nonuniform thickness around the abdominal cavity, which contains the VF. Our VF algorithm uses measurements of the total abdominal thickness, based on X-ray attenuation, and the width of the SF layer along the lateral extent of the abdomen along with empirically derived geometric constants to estimate the quantity of SF in the android region. VF is computed by subtracting SF from the total AF in the android region. The geometric assumptions of the model are based on comparing DXA and CT image volumes from a training set of images obtained from two independent clinical sites.

**Statistical methods**

Continuous variables were expressed as mean ± 1 s.d. Measurements were compared using paired *t*-tests with critical value of *P* = 0.05 used for assessing significant differences. Bland–Altman analysis was used to assess magnitude bias in the sample as a whole. Subgroup analysis was conducted to assess agreement in men and women separately. Pearson’s correlation coefficients were computed comparing DXA VF to clinical parameters of interest.

**RESULTS**

**Table 1** describes the study cohort. Five of the study subjects were excluded because of defects in the CT scan (metal artifacts, no iliac crest present). A subsample of males (*n* = 10) was included in the VF algorithm development cohort. The remaining 109 subjects (61 females and 48 males) represented the validation cohort. All results reported are for the validation cohort only that consisted of 100 whites, 5 Hispanics, and 4 Asians. There were no African-Americans in the group.

Due to the lack of practical selection techniques, subjects were not recruited on the basis of VF volume, albeit for the purposes of validation, a wide range of VF values is ideal to demonstrate utility of the measurement tool in a clinically relevant population. **Figure 2** shows the distribution of VF volume among the subjects. Although the distribution is skewed, there was a wide range, with values ranging from 42 to 4,126 cm<sup>3</sup> in females and 183 to 3,846 cm<sup>3</sup> in males.

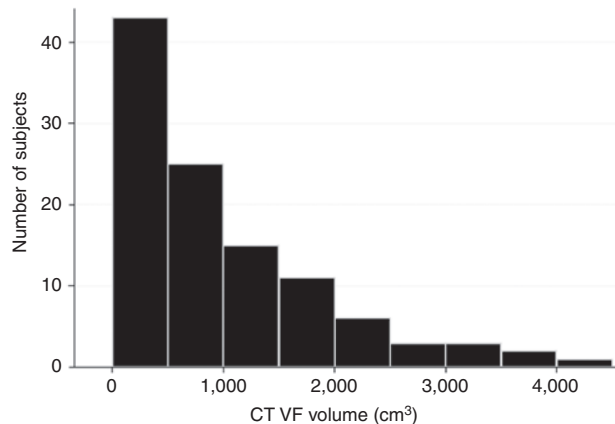
The primary endpoint of this study was agreement between DXA estimated and CT measured VF volume (**Figure 3**). The coefficient of determination (*r*<sup>2</sup>) for regression of CT on DXA values was 0.959 for females, 0.949 for males and 0.957 combined. The 95% confidence interval for *r* was 0.968 to 0.985 for the combined data (**Figure 3a**).

Bland–Altman analysis was conducted to characterize differences between DXA and CT VF measurements over the range of VF volumes included in the analysis. The 95% confidence interval for the mean of the differences between CT and DXA VF volume was –96.0 to –16.3 cm<sup>3</sup>. Bland–Altman bias (CT as standard method) was +67 cm<sup>3</sup> for females and +43 cm<sup>3</sup> for males. The 95% limits of agreement were –339 to +472 cm<sup>3</sup>

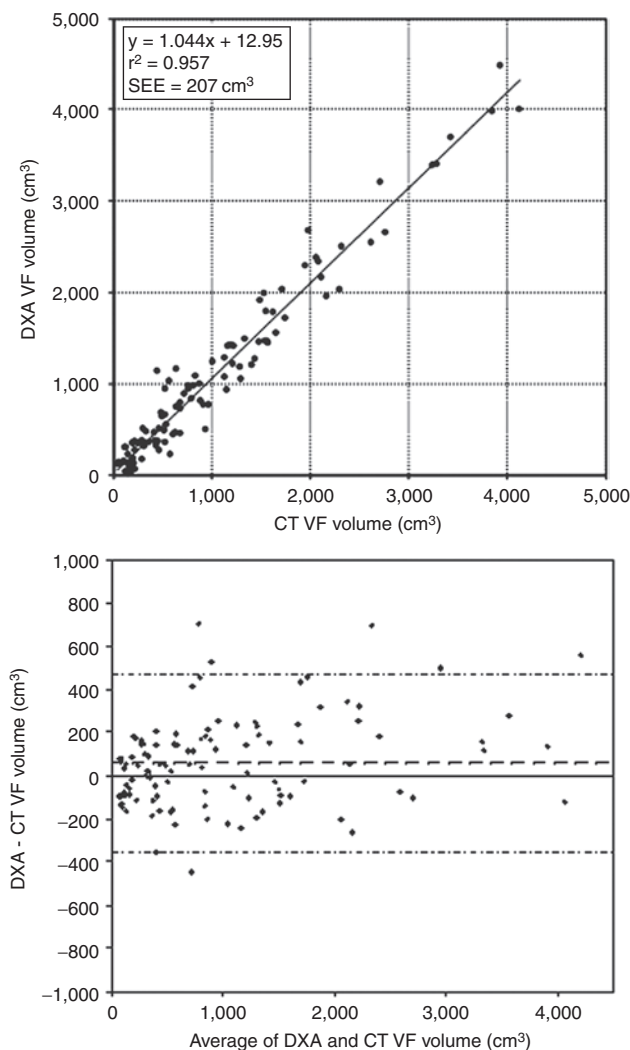
**Table 1** Descriptive statistics in the validation subjects (mean ± 1 s.d.)

Variable	Female ( <i>n</i> = 61)	Male ( <i>n</i> = 48)
Age (years)	48.5 ± 14.3	50.8 ± 13.4
Height (cm)	164.5 ± 6.7	177.9 ± 6.7
Weight (kg)	72.5 ± 14.4	84.8 ± 14.5
BMI (kg/m <sup>2</sup> )	26.7 ± 4.7	26.7 ± 3.5
Waist (cm)	87.6 ± 14.3	95.3 ± 10.5
Waist/hip	0.81 ± 0.08	0.89 ± 0.08
DXA AF (cm <sup>3</sup> )	2,310 ± 1,450	2,334 ± 1,130
DXA SF (cm <sup>3</sup> )	1,650 ± 810	1,010 ± 469
DXA VF (cm <sup>3</sup> )	800 ± 960	1,382 ± 946
CT VF (cm <sup>3</sup> )	730 ± 870	1,337 ± 900

AF, abdominal fat; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; VF, visceral fat.



**Figure 2** Histogram of visceral fat (VF) volumes measured by computed tomography (CT). This data highlights the wide distribution of VF within our population of subjects with BMI 20–40 kg/m<sup>2</sup>.



**Figure 3** Comparison of CT and DXA VF. Top: Correlation plot of dual-energy X-ray absorptiometry (DXA) visceral fat (VF) validation data against computed tomography (CT) for the combined dataset. Bottom: Bland–Altman plot of DXA VF validation data against CT for the combined dataset. SEE is defined as standard error of estimate = sqrt (regression error mean square).

for females and  $-379$  to  $+465$   $\text{cm}^3$  for males. Combined, the bias was  $+567$   $\text{cm}^3$  with 95% limits of agreement of  $-355$  to  $+468$   $\text{cm}^3$  (Figure 3b).

We further explored the relationships between VF and several other indices of total and central adiposity: BMI, waist circumference, waist-to-hip ratio, total DXA-derived AF, and DXA-derived SF. Whereas the DXA VF values were significantly correlated to varying degrees with all other indices, the scatter was large. Figure 4 shows the correlations between DXA VF values and BMI, waist circumference, waist-to-hip ratio, and DXA AF. Figure 5 shows the weak association between DXA-derived VF and SF.

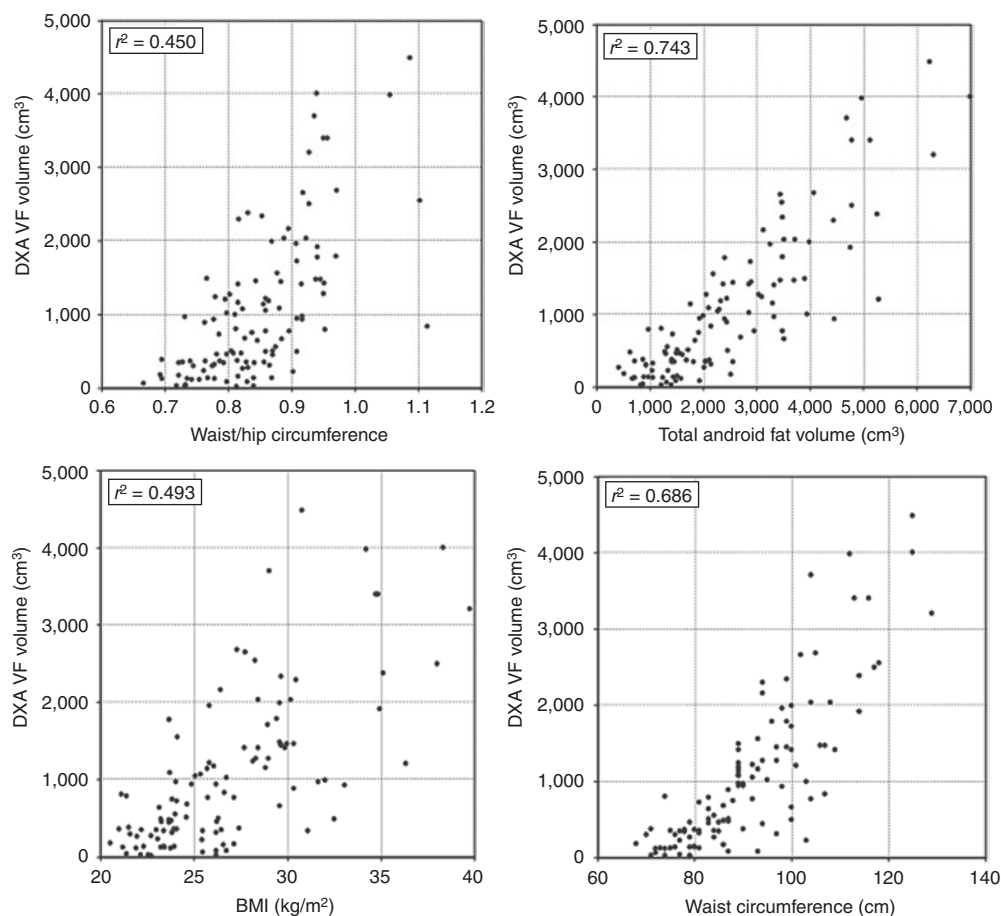
## DISCUSSION

In this report, we describe a new fully automated approach to quantify VF using DXA. We validated this method against CT, which is one of the current gold standards for quantifying VF. There was a strong agreement between DXA and CT across both genders and a wide range of BMI's. The average difference between techniques was  $56$   $\text{cm}^3$ , which is small relative to the average VF observed in our subjects ( $\sim 1$  kg). Relative to waist circumference, a common surrogate marker for abdominal obesity, the DXA values were better correlated with CT VF ( $r^2 = 0.957$  vs.  $0.686$ ). This is likely due to the inability of waist

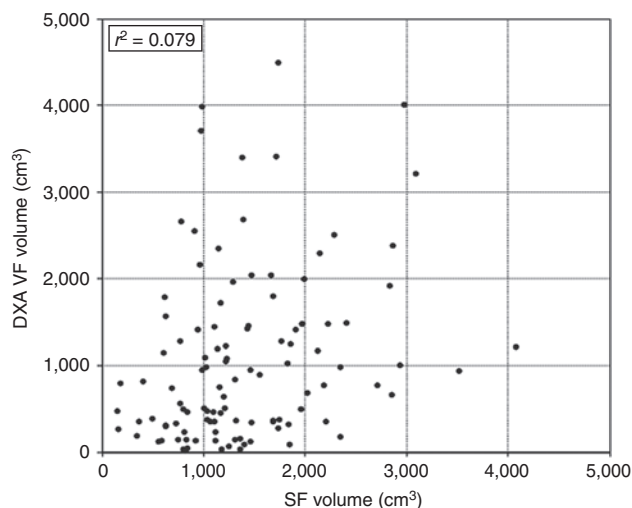
circumference to discriminate between VF and SF, which were not well correlated with each other in our study population.

DXA offers several advantages relative to CT or MRI for the measurement of VF. The cost of a DXA instrument is substantially lower than that of CT or MRI. Having such a system within an office-based practice or a research enterprise will, therefore, be more cost-effective and efficient rather than sharing a hospital-based CT or MRI system. DXA units can also be installed in a standard 100 sq. ft. room. The VF analysis is generated automatically soon after the total body scan, allowing the clinician to immediately access the VF information and communicate results (including images) to the patient while they are still in the office. DXA also exposes subjects to a much lower radiation dose relative to volumetric CT ( $0.96$   $\mu\text{Sv}$  for a Standard Mode Total body DXA exam vs.  $3,100$   $\mu\text{Sv}$  of radiation for an abdominal CT scan), making it suitable for repeated measurements. Whereas MRI has the advantage of no ionizing radiation, it has drawbacks that make it unattractive for incorporation into use for routine screening including expense, procedure time, and availability of systems. Consequently DXA could be used as a low-cost screening tool for quantification of VF and other adipose tissue in the clinical setting.

VF is now recognized as a risk factor for the metabolic syndrome, diabetes, and cardiovascular disease (1–8). Interestingly



**Figure 4** Correlation plots for dual-energy X-ray absorptiometry (DXA)-estimated visceral fat (VF) and BMI, waist circumference, waist-to-hip ratio, and DXA-estimated abdominal fat (AF).



**Figure 5** Correlation plot between dual-energy X-ray absorptiometry (DXA)-estimated visceral fat (VF) and subcutaneous fat (SF).

even in nonobese individuals it has been associated with hypertension, abnormal glucose tolerance, insulin resistance, metabolic syndrome, and low high-density lipoprotein levels (9,32–39). The exact reason for the propensity of VF to be associated with metabolic and cardiovascular abnormalities remains speculative, but compared to SF, VF is more metabolically active, more sensitive to lipolysis, more resistant to insulin, and has a greater capacity to take up glucose and generate free fatty acids (40). It is inversely correlated with adiponectin (41) and directly correlated with leptin and high-sensitivity C-reactive protein (37). VF is also more sensitive to weight loss and to effects of drugs such as pioglitazone (42).

#### Study limitations

There are several limitations in this study. First, while enrollment for the study was open, we had a small representation of nonwhite subjects, which is consistent with Oregon demographics (1.8% African American, 3.7% Asian, and 1.4% American Indian). However, racial identity was not considered to be among the most important recruiting criteria, since the basic assumptions of the VF algorithm require only an elliptical distribution of abdominal fat. Whereas, to our knowledge, there is no evidence that this assumption is specific to one ethnic group, larger scale studies need to be done in different ethnic groups to confirm the generalizability of our algorithm.

Second, we also did not include morbidly obese (BMI >40 kg/m<sup>2</sup>) or subjects under age 18 in this trial. It may be useful to expand into these populations in the future. Finally, since our DXA VF measurement is fully automated, it cannot be tested for observer variability. However, in a series of phantom studies, precision estimates accounting for inter- and intrascanner differences were ~40 g on a 1 kg VF mass.

#### Summary

Heretofore, there has been no readily available method to quantify VF. Hence crude measures such as BMI, waist circumference, and the waist-to-hip ratio have been used to obtain an

assessment of metabolic and cardiovascular risk. As can be seen from our results, these measurements do not reflect VF in a reliable manner and, importantly, SF has no significant relation with VF. A more reliable measurement of both metabolic and cardiovascular risk could potentially result from a direct measurement of VF. Further studies are needed to determine whether VF estimation offers incremental value to other more standard measures of metabolic and cardiovascular risk in patients.

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#### DISCLOSURE

M.P.R., W.K.W., and D.L.E. are employees of the funding company, GE Healthcare, or its affiliates. All the other authors declared no conflict of interest.

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