Association of Adipose Tissue Distribution With Type 2 Diabetes in Breast Cancer Patients

Jia Qi, Hui Hu, Lusine Yaghjyan, Lejun An, Harris A Kalim, Erinn O Cooke and Ting-Yuan David Cheng

1School of Population and Public Health, The University of British Columbia, Vancouver, BC, Canada. 2Department of Epidemiology, College of Public Health and Health Professions & College of Medicine, University of Florida, Gainesville, FL, USA. 3Department of Hypertension, Chinese Medicine Hospital of the Xinjiang University of Medicine, Urumqi, China. 4Department of Radiology, College of Medicine, University of Florida, Gainesville, FL, USA.

ABSTRACT

PURPOSE: We examined the association of adipose tissue distribution with type 2 diabetes (T2D) in breast cancer patients.

METHODS: Participants (N = 238) diagnosed with breast cancer at 20-75 years old who received breast cancer treatment at a major hospital from January 1, 2012, to December 31, 2017, with at least one completed and identifiable abdominal or pelvic computed tomography (CT) scan and data regarding race and ethnicity were included. Thirty-two breast cancer patients were identified as T2D patients after their breast cancer diagnoses. The adipose tissue distribution (visceral fat area [VFA], subcutaneous fat area [SFA], and the ratio of VFA to SFA [VFA/SFA]) was quantified on CT images of the third lumbar vertebra. T2D status was retrieved from patients’ electronic medical records. The association of adipose tissue distribution with T2D in women with breast cancer was examined using multivariable logistic regression.

RESULTS: Participants with T2D had significantly smaller SFA compared to those without T2D (odds ratio [OR] = 0.88, 95% confidence interval [95% CI] = 0.81-0.96, per 10 cm² SFA). A positive association of VFA/SFA ratio with T2D was observed (OR = 19.57, 95% CI = 3.26-117.42, per unit VFA/SFA), although the estimate was imprecise.

CONCLUSIONS: The amount of subcutaneous adipose tissue was inversely associated with T2D, and the ratio of the amount of visceral adipose tissue to the amount of subcutaneous adipose tissue was positively associated with T2D in breast cancer patients.

KEYWORDS: Adipose tissue distribution, type 2 diabetes, breast cancer

Introduction

Approximately 16% of breast cancer patients have type 2 diabetes (T2D), and previous research has suggested that T2D is associated with a worse prognosis of breast cancer. This association can be explained by the evidence that T2D is characterized by insulin resistance, which can result in the excessive secretion of insulin, and high levels of insulin are mitogenic for breast cancer cells.

Although obesity is an established risk factor of T2D, to what extent the distribution of fatness is associated with T2D is less clear. Obesity is commonly defined by body mass index (BMI). Nevertheless, this aggregate body mass measurement may not accurately reflect body fatness or adiposity because it is influenced by other body components such as bone and muscle. For instance, high BMI does not always represent high adiposity because BMI can be masked by muscularity. Moreover, some studies revealed that different types of excess fat, such as visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), were different in several aspects. For example, VAT has a greater ability to release free fatty acids that can increase blood glucose, whereas SAT more avidly absorbs free fatty acids. Thus, although measuring BMI is more convenient, adipose tissue distribution is more accurate for assessing obesity. Currently, both computed tomography (CT) and magnetic resonance imaging (MRI) provide high accuracy and reproducibility for measuring the distribution of adipose tissue. Compared with MRI, the operation time of CT is shorter, which can help to obtain clearer images of organs and tissues in action.

The purpose of this study was to explore the association of adipose tissue distribution with T2D in a sample of breast cancer patients. Although previous studies suggested that adipose tissue distribution was associated with the occurrence of T2D, they did not specifically examine breast cancer patients as their metabolism might be different from those without breast cancer. Our hypothesis was that the amount of VAT, but not SAT, was positively associated with T2D in breast cancer patients.
Materials and Methods

Study population

After obtaining approval from the Institutional Review Board of the University of Florida (IRB201800102), women diagnosed with breast cancer who received breast cancer treatment at the University of Florida Health Shands Hospital from January 1, 2012, to December 31, 2017, were identified for this cross-sectional study by using the electronic medical record system. Breast cancer diagnosis was defined using the International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes (174 and C50, respectively). Participants were limited to be 20-75 years old at the time of diagnosis and have at least one abdominal or pelvic CT scan taken after the diagnosis of breast cancer in the archive. For patients with multiple scans, the scan taken closest to the breast cancer diagnosis was selected. From 296 patients meeting these criteria, we further excluded those with incompletely recorded CT images at the third lumbar vertebra (L3) (n = 15), unidentifiable L3 CT images (n = 19), and missing demographic information, including race and ethnicity (n = 2). Breast cancer patients who had T2D before their diagnosis of breast cancer and whose CT scans were taken after the diagnosis of T2D were also excluded (n = 22). The final sample included 238 women, of whom 32 patients had a new onset of T2D and 206 patients were free of T2D since the breast cancer diagnosis (Figure 1).

Adipose tissue distribution measurement

As independent variables in this study, visceral fat area (VFA) and subcutaneous fat area (SFA) were measured by a single investigator blinded to participants’ demographic information and T2D status. As the amount of adipose tissue and skeletal muscle derived from the L3 area are representative of the amount in the whole body (Pearson correlation coefficient \( r = 0.927 \) for adipose tissue and 0.855 for skeletal muscle), \(^\text{20}\) L3 CT images were visually selected from patients’ whole abdominal or pelvic CT scans for image segmentation and measurement using the Sante DICOM Viewer (version 8.1.8, OnePacs, Palo Alto, California). For patients who had more than one CT scan during their breast cancer treatment, the CT scan taken closest to the time of breast cancer diagnosis was selected. Slice-O-Matic (version 5.0, TomoVision, Magog, Quebec, Canada) was used to perform adipose tissue segmentation. Adipose tissue was identified by tissue-specific Hounsfield Units (HU) from –190 HU to –30 HU, \(^\text{21}\) and VAT to the amount of SAT (VFA/SFA) was a risk factor for T2D, \(^\text{22}\) VFA/SFA was also treated as an independent variable in this study.

Type 2 diabetes status

The outcome data of interest, T2D status, were retrieved from patients’ electronic medical records. As all participants had been required to test for T2D, T2D patients were directly identified using the ICD codes of T2D diagnosis.

Covariates

Several characteristics of breast cancer patients were considered as potential confounders in this study. Age, race (African American/black or white) and ethnicity (Hispanic or non-Hispanic) were directly retrieved from patients’ electronic medical records. Muscle areas (MAs) in cm\(^2\) were measured based on patients’ L3 CT images using the CT segmentation method, and muscle tissue-specific HUs were measured from –29 HU to 150 HU. \(^\text{21}\) As participants’ waist circumferences (WCs) had not been recorded in the electronic medical record system, they were also measured on the L3 CT images.

Statistical analysis

To examine the representativeness of the study sample, we compared the distributions of the demographic characteristics and tumor stage of the study sample and all female breast cancer patients (n = 1632) who were included in the University of Florida Tumor Registry from January 1, 2012, to December 31, 2017, with the data on race, ethnicity, and age (between 20 and 75 years old) at the time of diagnosis. Chi-square test or Fisher exact test was used for categorical variables, including race, ethnicity, and tumor stage (if any cell had an expected count less than 5, Fisher exact test was used). T test was used for the comparison of age distributions between these 2 groups.

Distributions of the demographic characteristics and body measurements of breast cancer patients with and without T2D in the study sample were compared using \( \chi^2 \) test or Fisher exact test for categorical variables, including race and ethnicity, depending on their statistical characteristics. T test was used for the comparison of numerical variables, including age, WC, MA, VFA, SFA, and VFA/SFA. The correlation coefficients between body measurements (WC, MA, VFA, SFA, and VFA/SFA) were assessed using Pearson correlation.

Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for T2D in relation to VFA, SFA, and VFA/SFA. As 1 cm\(^2\) was too small to have clinical significance, analyses were conducted with a 10-unit increase (10 cm\(^2\)) in VFA and SFA. Further analyses were conducted with adipose tissue measures categorized into quartiles, in which Wald \( \chi^2 \) test was applied to examine linear trends. As previous studies reported that age, race, ethnicity, WC, and MA...
were associated with both adipose tissue distribution and T2D.23-27 These variables were all included in logistic regression models to control for potential confounding. Previous research has indicated that race might modify the relationship between adipose tissue distribution and T2D.25 Thus, this potential effect modifier was tested using likelihood ratio test. All tests were 2-sided, and their statistical significance was judged at 5%. Statistical analyses were performed using the Statistical Analysis System (SAS, version 9.4, SAS, Cary, North Carolina).

Results
This study included 238 women with breast cancer. The comparisons of the demographic characteristics and tumor stage distributions between the study sample and general breast cancer patients are shown in Table 1. The participants in the study sample were significantly older than the general breast cancer patients (60.3 vs 57.7 years, \( P < .0001 \)), and their racial distribution was significantly different from that of the general breast cancer patients (\( P = .0093 \)). The difference in tumor stage distributions between these 2 groups was also statistically significant (\( P < .0001 \)). Regarding breast cancer patients who had information on tumor stage, the majority of the participants in the study sample were in stage I and stage II breast cancer (16.0% for both stages), while the majority of general breast cancer patients were in stage I (36.4%). Moreover, the proportions of women in the study sample who were in stage III and stage IV were larger than that of the general breast cancer patients (9.7% vs 4.7%, 13.9% vs 6.4%, respectively).
The distributions of demographic characteristics of the study sample by T2D status are shown in Table 2. There was a statistically significant difference in the racial distributions between participants with T2D and participants without T2D ($P = .0329$). Although the majority of both groups were white women (71.9% and 87.9%), the proportion of black breast cancer patients with T2D was larger than that in individuals without T2D (28.1% vs 12.1%). In terms of age and ethnicity, the participants with T2D and those without T2D had similar baseline distributions ($P = .1872$ and $P = .1352$, respectively).

The distributions of body measurements by T2D status are also shown in Table 2. Breast cancer patients with T2D had significantly larger WCs than those without T2D (104.5 vs 98.7 cm, $P = .0354$). Moreover, significantly different from participants without T2D, women with T2D had larger VFA and VFA/SFAs (169.8 vs 132.5 cm$^2$, $P = .0143$, and 0.6 vs 0.5, $P = .0151$, respectively). The distributions of MA and SFA were not significantly different between these 2 groups ($P = .0862$ and $P = .5475$, respectively).

Except for VFA/SFA, which was correlated with only WC and VFA, all body measurements correlated with each other (Table 3).

Table 4 shows the results of multivariable regression examining the associations of VFA and SFA with T2D. After adjusting for age, race, ethnicity, WC, MA, and VFA, on average, participants who had T2D were 0.88 times as likely to have a 10 cm$^2$ larger SFA compared to breast cancer patients without T2D and this association was statistically significant (OR = 0.88, 95% CI = 0.81-0.96) (Model 1). In the model with the categorical variables of VFA and SFA, patients with versus without T2D were 0.07 times as likely to have SFA within Q4 than Q1 (OR = 0.07, 95% CI = 0.01-0.81) (Model 2). There was no association of VFA with T2D (see full models in Supplemental Table 1).

Table 5 shows the results of multivariable regression examining the association of VFA/SFA with T2D. Compared to...
breast cancer patients without T2D, patients with T2D were significantly 19.57 times more likely to have a one-unit higher VFA/SFA (OR = 19.57, 95% CI = 3.26-117.42) (Model 1). In the model of categorical variables, breast cancer patients with T2D were 6.34 times as likely to have VFA/SFA within Q4 than Q1 (OR = 6.34, 95% CI = 1.65-24.31) (Model 2) (see full models in Supplemental Table 2).

We observed that participants with T2D were likely to have larger WCs and likely to be black than white and Hispanic than non-Hispanic individuals (Supplemental Tables 1 and 2). The results of the likelihood ratio test suggested that race was not an effect modifier for the adiposity measurements and T2D (all P values for interaction >.05, data not shown).

**Discussion**

By using the CT scan segmentation technique, this study examined the association of adipose tissue distribution with T2D in breast cancer patients. We observed that for breast cancer patients, SAT was inversely associated with T2D, and VAT/SAT was positively associated with T2D.

---

**Table 2.** Demographic characteristics and body measurements of participants by type 2 diabetes status.

|                          | DIABETES (N = 32) | NON-DIABETES (N = 206) | P FOR DIFFERENCE |
|--------------------------|-------------------|------------------------|------------------|
| **Mean (SD)**            |                   |                        |                  |
| Age                      | 62.6 (8.9)        | 60.0 (10.6)            | .1872a           |
| WC (cm)                  | 104.5 (13.2)      | 98.7 (14.4)            | .0354a           |
| MA (cm²)                 | 139.0 (29.2)      | 130.5 (25.4)           | .0862a           |
| VFA (cm²)                | 169.8 (73.9)      | 132.5 (80.4)           | .0143a           |
| SFA (cm²)                | 313.9 (123.8)     | 297.9 (141.6)          | .5475a           |
| VFA/SFA                  | 0.6 (0.3)         | 0.5 (0.2)              | .0151a           |
| **Frequency (%)**        |                   |                        |                  |
| Race                     |                   |                        | .0329b           |
| White                    | 23 (71.9)         | 181 (87.9)             |                  |
| Black                    | 9 (28.1)          | 25 (12.1)              |                  |
| Ethnicity                |                   |                        | .1352c           |
| Non-Hispanic             | 30 (93.8)         | 203 (98.5)             |                  |
| Hispanic                 | 2 (6.3)           | 3 (1.5)                |                  |

Abbreviations: MA, muscle area; SFA, subcutaneous fat area; VFA, visceral fat area; WC, waist circumference.

* *T* test.

* *χ²* test.

* Fisher exact test.

**Table 3.** Pearson correlation coefficients between CT image–based measurements.

|                      | WC (CM) | MA (CM²) | VFA (CM²) | SFA (CM²) |
|----------------------|---------|----------|-----------|-----------|
| MA (cm²)             | 0.64    |          |           |           |
|                      | *P < .0001* |            |           |           |
| VFA (cm²)            | 0.77    | 0.51     |           |           |
|                      | *P < .0001* | *P < .0001* |            |           |
| SFA (cm²)            | 0.88    | 0.55     | 0.56      |           |
|                      | *P < .0001* | *P < .0001* | *P < .0001* |            |
| VFA/SFA              | 0.21    | 0.12     | 0.69      | -0.12     |
|                      | *P = .0014* | *P = .0603* | *P < .0001* | *P = .0676* |

Abbreviations: CT, computed tomography; MA, muscle area; SFA, subcutaneous fat area; VFA, visceral fat area; WC, waist circumference.
Previous studies reported that VAT was positively associated with T2D,14-18 but our study did not find any significant association of VAT with T2D. This inconsistency could be due to the metabolism of breast cancer patients being different from that of people without breast cancer.19 Researchers have found that VAT secretes retinol-binding protein 4, which can result in insulin resistance.28 Cortisol accelerates the breakdown of the protein.29 In healthy people, cortisol levels are usually highest before awakening and decrease during the day, but breast cancer patients’ cortisol levels are consistently high.30 This difference in cortisol metabolism between people with and without breast cancer may explain why we did not find any significant association of VAT with T2D in breast cancer patients. Mechanistic studies are needed to confirm this hypothesis. Other findings from our study were consistent with previous research. A cross-sectional study assessing adipose tissue in MRI scans found an inverse association between SAT and T2D.30 The inverse association could be explained

Table 4. Associations of the visceral fat area and the subcutaneous fat area with type 2 diabetes status (n=238).a

| EXPOSURE VARIABLE | MODEL 1 (CONTINUOUS) OR (95% CI) | MODEL 2 (CATEGORICAL) OR (95% CI) |
|-------------------|----------------------------------|----------------------------------|
| VFAb              | Per 10 units (10 cm²) 1.01 (0.41-2.47) | – |
|                   | Q1 – Reference |  |
|                   | Q2 – 3.65 (0.60-22.09) |  |
|                   | Q3 – 9.50 (1.50-60.17) |  |
|                   | Q4 – 4.52 (0.53-38.56) |  |
|                   | P for linear trend – .07 |  |
| SFAc              | Per 10 units (10 cm²) 0.88 (0.81-0.96) | – |
|                   | Q1 – Reference |  |
|                   | Q2 – 1.03 (0.21-5.17) |  |
|                   | Q3 – 0.34 (0.05-2.34) |  |
|                   | Q4 – 0.07 (0.01-0.81) |  |
|                   | P for linear trend – .06 |  |

Abbreviations: CI, confidence interval; OR, odds ratio; SFA, subcutaneous fat area; VFA, visceral fat area.

Table 5. Association of the ratio of visceral fat area to the subcutaneous fat area with type 2 diabetes status (N=238).a

| EXPOSURE VARIABLE | MODEL 1 (CONTINUOUS) OR (95% CI) | MODEL 2 (CATEGORICAL) OR (95% CI) |
|-------------------|----------------------------------|----------------------------------|
| VFA/SFAb          | Per unit 19.57 (3.26-117.42) | – |
|                   | Q1 – Reference |  |
|                   | Q2 – 0.80 (0.28-2.32) |  |
|                   | Q3 – 1.03 (0.34-3.14) |  |
|                   | Q4 – 6.34 (1.65-24.31) |  |
|                   | P for linear trend – <.01 |  |

Abbreviations: CI, confidence interval; OR, odds ratio; SFA, subcutaneous fat area; VFA, visceral fat area.

Table 4. Associations of the visceral fat area and the subcutaneous fat area with type 2 diabetes status (n=238).a

Table 5. Association of the ratio of visceral fat area to the subcutaneous fat area with type 2 diabetes status (N=238).a
by the fact that SAT can absorb free fatty acids to decrease blood glucose. In the Framingham Offspring and Third Generation cohorts, higher versus lower ratio of VAT/SAT was associated with insulin resistance and risk of T2D. The biological plausibility behind this association might be that VAT/SAT could be positively associated with lipodystrophy, and this lipid metabolism disorder would be followed by insulin resistance and T2D.

Our finding in the positive relationship of WC and black and Hispanic race/ethnicity with diabetes is consistent with the literature. Previous studies also supported the positive association of WC with insulin resistance and T2D, although the research in breast cancer patients is limited. It is to note that the WC measurement in our study was based on CT images in which a patient was resting. The WC measurement could differ from that taken in a standing position. However, any bias that could be introduced due to the difference should be minimal because supine WC and standing WC were highly correlated.

Our study was among the first examining the association of adipose tissue distribution with T2D specific to women with breast cancer. The strengths of the study included that the CT scan segmentation technique used to measure adipose tissue distribution in our study had high accuracy and reliability. Moreover, to maintain the accuracy and objectivity of this research, CT scan measurement was performed by a single investigator blinded to participants’ demographic information and T2D status.

However, several limitations of this study should also be considered. First, the sample size of this study was small. The findings should be considered preliminary, and replications with a larger sample size are warranted. In addition, the study sample was selected depending on the availability of clinical CT scans; thus, it was not probabilistically selected. The distributions of age, race, ethnicity and tumor stage of the participants in the study sample were different from those of the general breast cancer patients. Therefore, the generalizability of this study was limited. Another shortcoming was that BMI and tumor characteristics were not adjusted for in the regression models because both variables had a large proportion of missing data. Thus, the validity of the findings might be influenced by potential confounding. Moreover, because of the limitation of our data, we were unable to distinguish incident and recurrent breast cancer patients. Furthermore, information on treatments of breast cancer and diabetes, some of which can cause weight loss, was unavailable. Because of these limitations, the findings of our study should be considered preliminary.

In conclusion, we observed that SAT was inversely associated with T2D and that the VAT/SAT ratio was positively associated with T2D in female breast cancer patients. Further studies are warranted to explore these associations in larger population-based studies with a prospective design and more comprehensive data. Our findings, if confirmed, will be important for T2D prevention and prognosis improvement in breast cancer patients.

Acknowledgements
We would like to acknowledge Integrated Data Repository team, part of the Clinical and Translational Science Institute (CTSI) at the University of Florida, for assisting the project.

Author Contributions
J.Q designed the study, collected data, analyzed data, drafted the manuscript, and had primary responsibility for final content; T.-Y.D.C. provided essential materials and funding; H.A.K. and E.O.C. assisted data collection; H.H., L.Y., L.A. provided critical comments on study design, statistical methods, and manuscript preparation. All authors read and approved the final manuscript.

Ethical Approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of the University of Florida (reference number: IRB201800102) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent
The requirement of informed consent was waived by the Institutional Review Board of the University of Florida.

ORCID iDs
Jia Qi https://orcid.org/0000-0003-4100-5302
Ting-Yuan David Cheng https://orcid.org/0000-0002-4105-828X

Supplemental Material
Supplemental material for this article is available online.

REFERENCES
1. Wolf I, Sadetzki S, Catane R, et al. Diabetes mellitus and breast cancer. Lancet Oncol. 2005;6:103-111.
2. Lipsonthe LL, Goodwin PJ, Zimmam B, McLaughlin JR, Hux JE. The impact of diabetes on survival following breast cancer. Breast Cancer Res Treat. 2008;109:389-395.
3. Kaplan MA, Pekkoly Z, Kucukoner M, et al. Type 2 diabetes mellitus and prognosis in early stage breast cancer women. Med Oncol. 2012;29:1576-1580.
4. World Health Organization. Obesity: preventing and managing the global epidemic: report of a WHO consultation on obesity. https://apps.who.int/iris/handle/10665/63854?show=full. Updated 1998. Accessed December 21, 2018.
5. Bonack HR, Stokes A, Fox MP, et al. Stratified probabilistic bias analysis for BMI-related exposure misclassification in postmenopausal women. Epidemiology. 2018;29:604-613.
6. Caan BJ, Feliciano EMC, Prado CM, et al. Association of muscle and adiposity measured by computed tomography with survival in patients with nonmetastatic breast cancer. JAMA Oncol. 2018;4:798-804.
7. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obes Res. 2010;11:11-18.
8. Freedland ES. Role of a critical visceral adipose tissue threshold (CVATT) in metabolic syndrome: implications for controlling dietary carbohydrates: a review. Nutr Metab. 2004;1:112.
9. Akoumanakis I, Akawi N, Antoniades C. Exploring the crosstalk between adipose tissue and the cardiovascular system. Korean Circ J. 2017;47:670-685.
10. Camhi SM, Bray GA, Bouchard C, et al. The relationship of waist circumference and BMI to visceral, subcutaneous, and total body fat: sex and race differences. Obesity. 2011;19:402-408.
11. Lee SY, Gallagher D. Assessment methods in human body composition. *Curr Opin Clin Nutr Metab Care*. 2008;11:566-572.

12. Schlett C, Hoffmann U. Identification and quantification of fat compartments with CT and MRI and their importance. *Radiology*. 2011;51:372-378.

13. Kim SH, Choi BI, Han JK, et al. Preoperative staging of uterine cervical carcinomas: comparison of CT and MRI in 99 patients. *J Comput Assist Tomogr*. 1993;17:633-640.

14. Boyko EJ, Fujimoto WY, Leonetti DL, Newell-Morris L. Visceral adiposity and risk of type 2 diabetes: a prospective study among Japanese Americans. *Diabetes Care*. 2000;23:465-471.

15. Haffner S. Sex hormones, obesity, fat distribution, type 2 diabetes and insulin resistance: epidemiological and clinical correlation. *Int J Obes Relat Metab Disord*. 2000;24:556-58.

16. Miyazaki Y, Glass L, Triplitt C, Wajcberg E, Mandarino LJ, DeFronzo RA. Abdominal fat distribution and peripheral and hepatic insulin resistance in type 2 diabetes mellitus. *Am J Physiol Endocrinol Metab*. 2002;283:E1135-1143.

17. Neeland IJ, Turer AT, Ayers CR, et al. Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. *JAMA*. 2012;308:1150-1159.

18. Ohlson LO, Larsson B, Svardsudd K, et al. The influence of body fat distribution on the incidence of diabetes mellitus: 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes*. 1985;34:1055-1058.

19. Demark-Wahnefried W, Hars V, Conaway MR, et al. Reduced rates of metabolism and decreased physical activity in breast cancer patients receiving adjuvant chemotherapy. *Am J Clin Nutr*. 1997;65:1495-1501.

20. Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol*. 2004;97:2333-2338.

21. Taksali SE, Caprio S, Dziura J, et al. Abdominal visceral and low abdominal subcutaneous fat. *J Clin Endocrinol Metab*. 2001;50:1134-1142. doi:10.2337/diabetes.50.5.1134.

22. Beasley LE, Koster A, Newman AB, et al. Inflammation and race and gender differences in computerized tomography-measured adipose depots. *Obesity*. 2008;16:2375-2381.

23. Lee SY, Gallagher D. Assessment methods in human body composition. *Curr Opin Clin Nutr Metab Care*. 2008;11:566-572.

24. TomoVision. SliceOmatic [computer program] Version 5.0. http://www.tomovision.com/products/sliceomatic.html. Updated 2015. Accessed December 28, 2018.

25. Herman WH, Myhre A, Violette N, et al. Differences in A1C by race and ethnicity among patients with impaired glaucos tolerance in the Diabetes Prevention Program. *Diabetes Care*. 2007;30:2453-2457.

26. Machann J, Thamer C, Schoedt B, et al. Age and gender related effects on adipose tissue compartments of subjects with increased risk for type 2 diabetes: a whole body MRI/MRS study. *MAGMA*. 2005;18:128-137.

27. Wei M, Gaskill SP, Haffner SM, Stern MP. Waist Circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexicans—A 7-year prospective study. *Obes Res*. 1997;5:16-23. doi:10.1002/j.1550-8288.1997.tb00278.x.

28. Golan R, Lefebvre J, Rudich A, et al. Abdominal Subcutaneous Fat. *Diabetes Care*. 2012;35:640-647. doi:10.2337/dc11-1583.

29. Gavi S, Stuart LM, Kelly P, et al. Retinol-binding protein 4 is associated with insulin resistance and body fat distribution in nonobese subjects without type 2 diabetes. *J Clin Endocrinol Metab*. 2007;92:1886-1890. doi:10.1210/jc.2006-1815.

30. Sephton SE, Saposky RM, Kraemer HC, et al. Diurnal cortisol rhythm as a predictor of breast cancer survival. *J Natl Cancer Inst*. 2000;92:994-1000. doi:10.1093/jnci/92.12.994.

31. Kaess B, Pedley A, Massaro J, Murabito J, Hoffmann U, Fox CS. The ratio of visceral to subcutaneous fat, a metric of body fat distribution, is a unique correlate of cardiometabolic risk. *Diabetologia*. 2012;55:2622-2630.

32. Taksali SE, Caprio S, Dziura J, et al. High visceral and low abdominal subcutaneous fat stores in the obese adolescent: a determinant of an adverse metabolic phenotype. *Diabetes*. 2008;57:367-371.

33. Garg A, Peshock RM, Fleckstein JL. Adipose tissue distribution patterns in patients with familial partial lipodystrophy (Dunnigan variety). *J Clin Endocrinol Metab*. 1999;84:170-174.

34. Davidson M. The disproportionate burden of diabetes in African-American and Hispanic populations. *Ethn Dis*. 2001;11:148-151.

35. Okosun IS, Cooper RS, Rotimi CN, Oustimehin B, Forrester T. Association of waist circumference with risk of hypertension and type 2 diabetes in Nigerians, Jamaicans, and African-Americans. *Diabetes Care*. 1998;21:1836-1842.

36. Wahrenberg H, Hertel K, Leijonhufvud B-M, et al. Use of waist circumference to predict insulin resistance: retrospective study. *BMJ*. 2005;330:1363-1364.

37. Waninge A, Ligthart KA, Kramer J, Hoere S, van der Schans CP, Haisma HH. Measuring waist circumference in disabled adults. *Res Dev Disabil*. 2010;31:839-847. doi:10.1016/j.ridd.2010.02.001.

38. Malin SK, Kashyap SR. Effects of metformin on weight loss: potential mechanisms. *Curr Opin Endocrinol Diabetes Obes*. 2014;21:323-329.